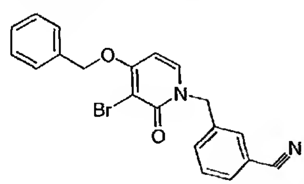
Preparation of 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile. 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(1.0 g, 3.6 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). α-Bromo-*p*-tolunitrile (0.85g, 4.3 mmol) was added followed by K_2CO_3 (0.59 g, 4.3 mmol). The resulting mixture was heated to 80 °C for 16 h. The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate (3 x 100 ml). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (0.65 g, 46%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 2H), 7.41-7.31 (m, 7H), 7.23 (d, J = 7.6 Hz, 1H), 6.11 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 5.18 (s, 2H). ES HRMS m/z 395.0404 (M+H $C_{20}H_{15}BrN_2O_2$ requires 395.0390).

Example 135

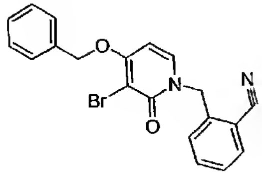
3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in example 134. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.54 (m, 3H), 7.45 (d, J = 7.6Hz, 1H), 7.43-7.31 (m, 5H), 7.26 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 1.6 Hz, 1H), 5.24 (s, 2H), 5.15 (s, 2H). ES HRMS m/z 395.0420 (M+H $C_{20}H_{15}BrN_2O_2$ requires 395.0390).

Example 136

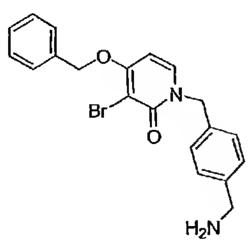
2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in example 134. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 1H); 7.63 (dd, J = 1.2, 8.0 Hz, 1H), 7.57 (dt, J = 1.2, 8.4 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H); 7.43-7.30 (m, 6H), 6.13 (d, J = 8.0 Hz, 1H,), 5.33 (s, 2H), 5.23 (s, 2H). ES HRMS m/z 395.0398 (M+H $C_{20}H_{15}BrN_2O_2$ requires 395.0390).

Example 137

1-[4-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one

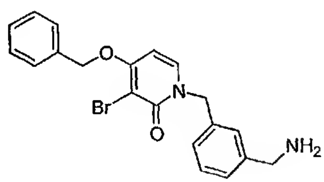


Preparation of 1-[4-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one. EXAMPLE 134 (100 mg, 0.25 mmol) was dissolved in tetrahydrofuran (2 mL) under N_2. Borane

dimethylsulfide complex (0.25 mL, 0.5mmol, 2M in tetrahydrofuran) was added. The reaction was then heated to 70°C and shaken overnight. The mixture was cooled and all the solvent was distilled under vacuum. The resulting residue was partitioned between ethyl acetate and 0.2 N NaOH, and extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and triturated with dichloromethane and hexane to give an off-white solid. (80 mg, 80%). ^1H NMR (400 MHz, d_6DMSO) δ 7.90 (d, J = 7.6 Hz, 1H); 7.43-7.21 (m, 9H), 6.70 (d, J=7.6 Hz, 1H), 5.29 (s, 2H), 5.08 (s, 2H), 3.71 (s, 2H). ES HRMS m/z 399.0721 (M+H $C_{20}H_{19}BrN_2O_2$ requires 399.0703).

Example 138

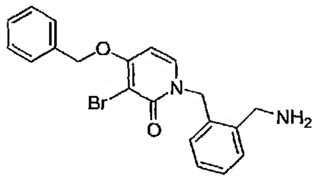
1-[3-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one



The title compound was prepared by a procedure essentially as described in Example 137 using the title compound of Example 135 as starting material. ^1H NMR (400 MHz, d_6DMSO) δ 7.90 (d, J = 7.6 Hz, 1H), 7.44-7.22 (m, 9H), 6.50 (d, J=7.6 Hz, 1H), 5.30 (s, 2H), 5.12 (s, 2H), 3.88 (s, 2H). ES HRMS m/z 399.0730 (M+H $C_{20}H_{19}BrN_2O_2$ requires 399.0703).

Example 139

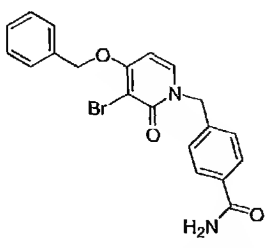
1-[2-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one



The title compound was prepared by a procedure essentially as described in Example 137 using the title compound of Example 136 as starting material. ^{1}H NMR (400 MHz, d_6DMSO) δ 7.88 (d, *J* = 8.0 Hz, 1H); 7.45-7.34 (m, 5H), 7.26- 7.21 (m, 3H); 6.85 (d, *J*=7.2 Hz, 1H), 6.53 (d, *J*=7.6 Hz, 1H), 5.32 (s, 2H), 5.12 (s, 2H), 3.90 (s, 2H). ES HRMS m/z 399.0699 (M+H $C_{20}H_{19}BrN_2O_2$ requires 399.0703).

Example 140

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide

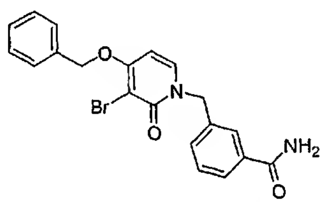


Preparation of 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide. EXAMPLE 134 (100 mg, 0.25 mmol) was added to a suspension of potassium fluoride (40% on alumina) in t-butyl alcohol, heated to 85°C, and stirred for 20h. The

alumina was removed by filtration and washed with dichloromethane and water. The resulting filtrate was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil. Trituration with dichloromethane and hexane gave a solid (11.5 mg, 11%). ^{1}H NMR (400 MHz, d_6DMSO) δ 7.94 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H); 7.43-7.29 (m, 7H), 6.51 (d, J=7.6 Hz, 1H), 5.31 (s, 2H), 5.16 (s, 2H). ES HRMS m/z 413.0541 (M+H $C_{20}H_{17}BrN_2O_3$ requires 413.0495).

Example 141

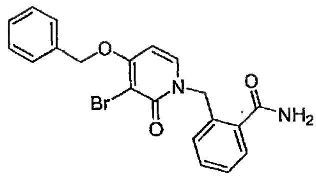
3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide



The title compound was prepared by a procedure essentially as described in Example 140 using the title compound of Example 135 as starting material. ^{1}H NMR (400 MHz, d_6DMSO) δ 7.95 (d, J = 7.6 Hz, 2H), 7.76 (m, 2H); 7.43-7.26 (m, 8H), 6.51 (d, J=7.6 Hz, 1H), 5.31 (s, 2H), 5.15 (s, 2H). ESHRMS m/z 413.0497 (M+H $C_{20}H_{17}BrN_2O_3$ requires 413.0495).

Example 142

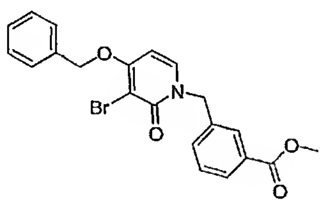
2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide



The title compound was prepared by a procedure essentially as described in Example 140 using the title compound of Example 136 as starting material. ^{1}H NMR (400 MHz, d_6DMSO) δ 7.78 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 1.6, 7.6 Hz, 1H); 7.45 (d, J=7.6 Hz, 2H); 7.44-7.32 (m, 5H), 7.15 (d, J=7.6 Hz, 1H), 6.49 (d, J=7.6 Hz, 1H), 5.39 (s, 2H), 5.30 (s, 2H). ES HRMS m/z 4413.0506 (M+H $C_{20}H_{17}BrN_2O_3$ requires 413.0495).

Example 143

Methyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate

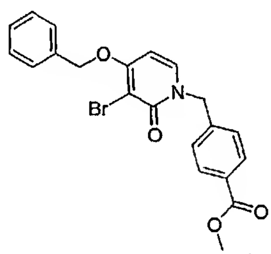


Preparation of Methyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate. EXAMPLE 134 (100 mg, 0.25 mmol) was suspended in methanol and cooled to 0°C. HCl (g) was bubbled through the mixture until saturated (~30 minutes). The reaction was warmed to ambient temperature and stirred for 4 hours. HCl and methanol were removed *in vacuo*, yielding an oil, that was purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (3 mg, 3%). ^{1}H NMR

(400 MHz, CD_3OD) δ 7.98 (*app* d, *J* = 8.0 Hz, 2H), 7.77 (*app* d, *J* = 8.0 Hz, 1H); 7.55 (*app* d, *J* = 8.0 Hz, 2H); 7.41-7.35 (m, 5H), 6.52 (d, *J* = 7.6 Hz, 1H), 5.31 (s, 2H), 5.27 (s, 2H); 3.88, (s, 3H). API-ES MS m/z 429.0 (M+H $C_{21}H_{18}BrNO_4$ requires 428.0492).

Example 144

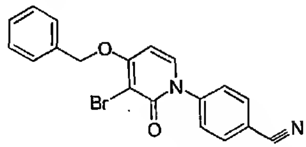
Methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate



The title compound was prepared by a procedure essentially as described in Example 143 using the title compound of Example 134 as starting material. ^1H NMR (400 MHz, CD_3OD) δ 7.94 (*app* d, *J* = 8.4 Hz, 2H), 7.76 (*app* d, *J* = 7.6 Hz, 1H); 7.46 (*app* d, *J* = 8.0 Hz, 2H); 7.39-7.35 (m, 5H), 6.51 (d, *J*=7.6 Hz, 1H), 5.31 (s, 2H), 5.26 (s, 2H); 3.88, (s, 3H). ES HRMS m/z 428.0492 (M+H $C_{21}H_{18}BrNO_4$ requires 428.0492).

Example 145

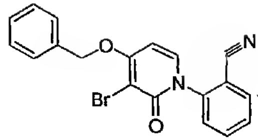
4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(100 mg, 0.36 mmol) was suspended in dimethylsulfoxide (5 mL), cesium carbonate (375 mg, 1.15 mmol) was added and the reaction was shaken for 5 minutes. 4-Fluorobenzonitrile (52 mg, 0.43 mmol was then added, the reaction was heated to 80°C, and stirred. Reaction was monitored by LC/MS, and after 4h was heated to 100°C and stirred for 16 hours. Reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (5 x 50 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (40 mg, 29%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.44-7.42 (m, 4H), 7.28 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 6.24 (d, J = 7.6 Hz, 1H); 5.31, (s, 2H). ES HRMS m/z 381.0230 (M+H $C_{19}H_{13}BrN_2O_2$ requires 381.0233).

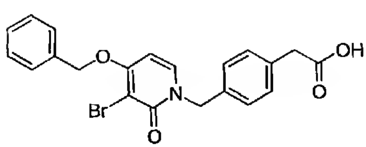
Example 146

2-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile



Preparation of 2-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(100 mg, 0.36 mmol) was suspended in dimethylsulfoxide (5 mL), cesium carbonate (375 mg, 1.15 mmol) was added and the reaction was shaken for 5 minutes. 4-Fluorobenzonitrile (52 mg, 0.43 mmol) was then added and the reaction was heated to 80°C with stirring. Reaction was monitored by LC/MS, and after 4h was heated to 100°C and stirred for 16 hours. The reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (5 x 50 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (18 mg, 13%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 1.2, 8.4 Hz, 1H), 7.73 (dt, J = 1.2, 8.0 Hz, 1H), 7.57 (dt, J = 0.8, 8.0 Hz, 1H), 7.50-7.36 (m, 6H), 7.27 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 8.0 Hz, 1H); 5.31 (s, 2H). ES HRMS m/z 381.0249 (M+H $C_{19}H_{13}BrN_2O_2$ requires 381.0233).Example 147

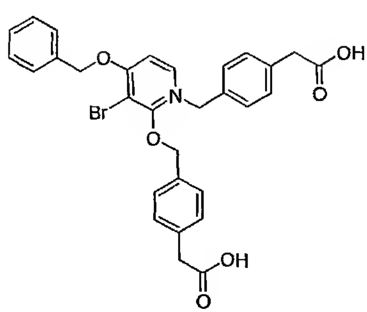
(4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetic acid



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(0.5g, 1.78 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). 4-(Bromomethyl)phenylacetic acid (0.5 g, 2.14 mmol) was added followed by K_2CO_3 (0.3 g, 2.14 mmol). The reaction was heated to 80°C and shaken for 16 hours, then heated to 100°C and shaken for 16 hours more. The reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (2 x 50 mL). The aqueous layer was acidified (pH 2) with 1N HCl and extracted with ethyl acetate (3 x 50 ml). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) followed by reversed phase chromatography (C_{18}, 0.1% aqueous trifluoroacetic acid /acetonitrile) to yield a white solid (25 mg, 3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 3H), 7.25-7.20 (m, 7H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.21 (s, 2H); 5.13, (s, 2H); 3.62, (s, 2H). ES HRMS m/z 428.0510 (M+H $C_{21}H_{18}BrNO_4$ requires 428.0492).

Example 148

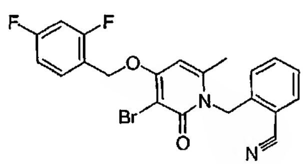
{4-[(4-(benzyloxy)-3-bromo-2-{[4-(carboxymethyl)benzyl]oxy}-1lambda^5-pyridin-1-yl)methyl]phenyl}acetic acid



Preparation of {4-[(4-(benzyloxy)-3-bromo-2-{[4-(carboxymethyl)benzyl]oxy}-1lambda^5-pyridin-1-yl)methyl]phenyl}acetic acid. The desired product was isolated by reversed phase chromatography (C_{18}, 0.1% aqueous trifluoroacetic acid/acetonitrile) using the preparation of Example 147 yielding a white solid (53 mg, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 3H), 7.27-7.24 (m, 6H), 7.20 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.4 Hz, 1H), 6.06 (d, J = 7.6 Hz, 1H), 5.21 (s, 2H); 5.11 (s, 2H); 5.11 (s, 2H); 3.63 (s, 2H); 3.58 (s, 2H). ES HRMS m/z 576.1009(M+H $C_{30}H_{28}BrNO_6$ requires 576.1016).

Example 149

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

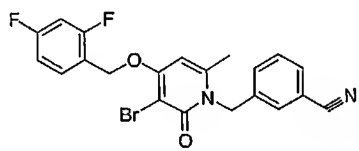


Preparation of 2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile. 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1*H*)-one (50 mg, 0.15 mmol) was dissolved in tetrahydrofuran (2 mL). α-Bromo-o-tolunitrile (44 mg, 0.23 mmol) was added followed by sodium hydride (7.2 mg, 0.18 mmol, 60% in mineral oil) and sodium iodide (56 mg, 0.38 mmol). The reaction was heated to 50°C and stirred for 16 hours. The reaction was filtered through Celite® and the filtrate was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with

ethyl acetate (4 x 10 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (25 mg, 37%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.0, 1.2 Hz, 1H); 7.58 (*app* q, *J* = 8.8 Hz, 1H); 7.52 (dt, *J* = 8.0 & 1.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H); 7.08 (d, *J* = 8.8 Hz, 1H), 7.00-6.93 (m, 1H); 6.89-6.84 (m, 1H); 6.05 (s, 1H), 5.57 (s, 2H), 5.22 (s, 2H); 2.28, (s, 3H). ES HRMS m/z 445.0335 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requires 445.0358).

Example 150

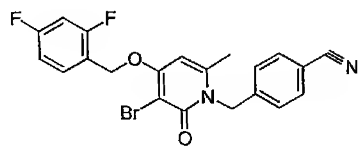
3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in Example 149 using 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (1 g, 3.0 mmol) as starting material. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61-7.55 (m, 2H); 7.45-7.41 (m, 3H); 6.98-6.94 (m, 1H); 6.89-6.84 (m, 1H); 6.03 (s, 1H), 5.36 (s, 2H), 5.22 (s, 2H); 2.30, (s, 3H). ES HRMS m/z 445.0349 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requires 445.0358)

Example 151

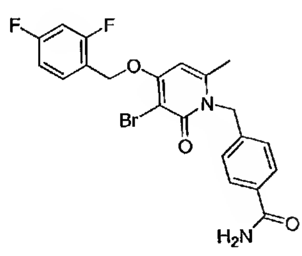
4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in Example 149 using 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (1 g, 3.0 mmol) as starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H); 7.62-7.56 (m, 1H); 7.27 (d, J = 8.8 Hz, 2H); 6.95 (*app* t, J = 8.4 Hz, 1H), 6.88-6.83 (m, 1H); 6.03 (s, 1H), 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 445.0359 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requires 445.0358).

Example 152

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

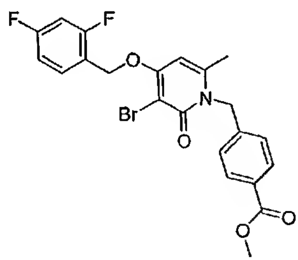


EXAMPLE 151 (50 mg, 0.11 mmol) was added to a suspension or potassium fluoride (40% on alumina) in t-butyl alcohol. The

reaction was heated to 90°C and stirred for 20 hours. Alumina was removed by filtration and washed with dichloromethane and water. The resulting filtrate was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated to an oil which was purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid, yielding the product (13 mg, 25%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (*app* d, J = 8.4 Hz, 2H), 7.58 (*app* q, J = 8.4 Hz, 1H); 7.24 (d, J = 8.4 Hz, 2H); 6.98-6.94 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.40 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0486 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463.0463).

Example 153

Methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate

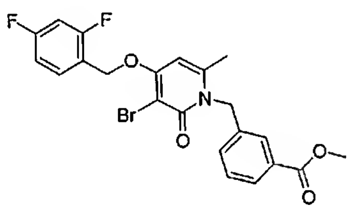


EXAMPLE 151 (50 mg, 0.11 mmol) was suspended in methanol and cooled to 0°C. HCl (g) was bubbled through the mixture until saturated (~30 minutes). Reaction was sealed, warmed to ambient temperature, and stirred for 2 hours. HCl and methanol were removed *in vacuo*, yielding an oil, that was purified by chromatography (silica gel, hexane/ethyl acetate)

to yield a white solid (19 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (*app* d, J = 8.4 Hz, 2H), 7.58 (*app* q, J = 8.0 Hz, 1H); 7.22 (d, J = 8.4 Hz, 2H); 6.95 (*app* dt, J = 1.5, 9.6 Hz, 1H), 6.89-6.83 (m, 1H), 6.00 (s, 1H); 5.41 (s, 2H), 5.21 (s, 2H); 3.90, (s, 3H); 2.27 (s, 3H). ES HRMS m/z 478.0461 (M+H $C_{22}H_{18}BrNO_4$ requires 478.0460).

Example 154

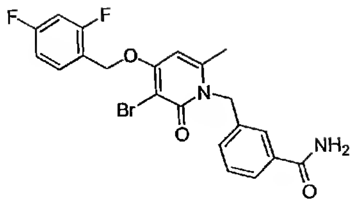
Methyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate



The title compound was prepared by a procedure essentially as described in Example 149 using the title compound of Example 150 as starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.92 (m, 1H); 7.84 (bs, 1H); 7.58 (*app* q, J = 8.0 Hz, 1H); 7.39-7.37 (m, 2H); 6.95 (*app* dt, J = 1.6, 8.4 Hz, 1H), 6.88-6.83 (m, 1H), 6.00 (s, 1H); 5.40 (s, 2H), 5.21 (s, 2H); 3.90, (s, 3H); 2.30 (s, 3H). ES HRMS m/z 478.0449 (M+H $C_{22}H_{18}BrNO_4$ requires 478.0460).

Example 155

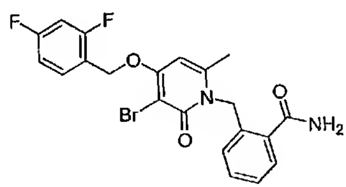
3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide



The title compound was prepared by a procedure essentially as described in Example 152 using the title compound of Example 150 as starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 2H), 7.57 (*app* q, J = 8.4 Hz, 1H); 7.42-7.34 (m, 2H); 6.98-6.92 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463.0463).

Example 156

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

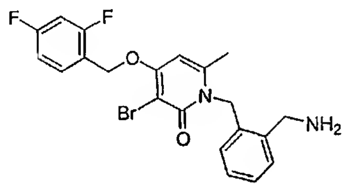


The title compound was prepared by a procedure essentially as described in Example 152 using the title compound of Example 149 as starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 2H), 7.57 (*app* q, J = 8.4 Hz, 1H); 7.42-7.34 (m, 2H); 6.98-6.92 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463.0463). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.56-7.55 (m, 2H); 7.32-7.25 (m, 2H); 7.00-6.94 (m, 1H), 6.88-6.84 (m, 1H); 6.81-6.79 (m, 1H) 6.11 (s, 1H); 5.51 (s, 2H), 5.24 (s, 2H); 2.43 (s, 3H). ESHRMS m/z 463.0467 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463.0463).

Example 157

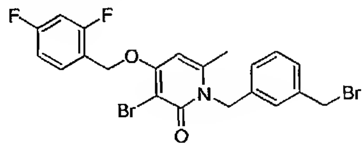
1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



EXAMPLE 149 (50 mg, 0.11 mmol) was dissolved in tetrahydrofuran (2 mL) under N_2. Borane-methyl sulfide complex (0.11 mL, 0.22 mmol, 2M in tetrahydrofuran) was added. The reaction was then heated to 70°C and shaken overnight. After cooling to ambient temperature, all the solvent was distilled under vacuum. The resulting residue was partitioned between ethyl acetate and 0.2 N NaOH, and extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with brine, and dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid, to give product (19 mg, 39%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.55 (m, 2H); 7.32-7.25 (m, 2H); 7.00-6.94 (m, 1H), 6.88-6.84 (m, 1H); 6.81-6.79 (m, 1H); 6.11 (s, 1H); 5.44 (s, 2H), 5.17 (s, 2H); 4.59 (s, 2H); 2.18 (s, 3H). ESHRMS m/z 449.0692 (M+H $C_{21}H_{19}BrF_2N_2O_2$ requires 449.0671).

Example 158

3-bromo-1-[3-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

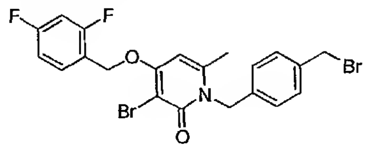


Preparation of 3-bromo-1-[3-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2 g, 6.06 mmol) was suspended in 1,4-dioxane (250 mL). α,α'-Dibromo-*m*-xylene (8 g, 30.3 mmol) was added followed by sodium hydride (0.3 g, 7.5 mmol, 60% in mineral oil). The reaction was heated to 60°C and stirred for 16 hours. The reaction was filtered through Celite® and the filtrate was concentrated to an oil that was partitioned between water and dichloromethane and extracted with dichloromethane (4 x 250 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (1.2g, 38%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (*app* q, J = 7.6 Hz, 1H); 7.28-7.25 (m, 2H); 7.17 (s, 1H); 7.08 (m,1H); 6.94 (*app* dt, J = 1.2, 9.6 Hz, 1H), 6.87-6.82 (m, 1H); 5.99 (s, 1H), 5.34 (s, 2H), 5.20 (s, 2H); 4.43 (s, 2H); 2.29 (s, 3H). ES HRMS m/z 511.9672 (M+H $C_{21}H_{17}Br_2F_2NO_2$ requires 511.9667).

Example 159

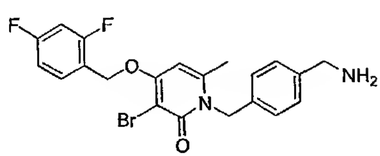
3-bromo-1-[4-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



The title compound was prepared by a procedure essentially as described in Example 158. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 2H), 7.57 (*app* q, J = 8.4 Hz, 1H); 7.42-7.34 (m, 2H); 6.98-6.92 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463.0463). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (*app* q, J = 7.6 Hz, 1H); 7.32(d, J = 8.0 Hz, 2H); 7.14 (d, J = 8.0 Hz, 2H); 6.94 (*app* t, J = 8.4 Hz, 1H), 6.87-6.82 (m, 1H); 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 4.44 (s, 2H); 2.29 (s, 3H). ES HRMS m/z 511.9683 (M+H $C_{21}H_{17}Br_2F_2NO_2$ requires 511.9667).

Example 160

1-[4-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

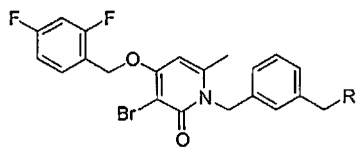


Example 159 (200 mg, 0.39 mmol) was suspended in methanol (3 mL) and cooled to -78 °C. Ammonia (g) was bubbled through the mixture for 30 minutes. The reaction vessel was sealed,

allowed to reach ambient temperature, and stirred for 4 hours. The solvent and ammonia were removed from the reaction *in vacuo* with stirring and the resulting oil was triturated with ether to yield a solid (174 mg, 99%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (q, *J* = 7.6 Hz, 1H); 7.40 (d, *J* = 8.0 Hz, 2H); 7.20 (d, *J* = 8.0 Hz, 2H); 7.03 (*app* t, *J* = 8.8 Hz, 2H), 6.51 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H); 4.07 (s, 2H); 2.36 (s, 3H). ES HRMS m/z 449.0673 ($C_{21}H_{19}BrF_2N_2O_2$ requires 449.0671).

Examples 161-168

The compounds of Examples 161-168 are prepared essentially according to the procedures set forth above for Examples 158-160 or by using the compound of Example 158:



Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 161	$-NH_2$	$C_{21}H_{19}BrF_2N_2O_2$	449.0671	449.0694
Ex. 162	morpholin-4-yl	$C_{25}H_{25}BrF_2N_2O_3$	519.1089	519.1132
Ex. 163	dimethylamino	$C_{23}H_{23}BrF_2N_2O_2$	477.0984	477.0991
Ex. 164	isopropylamino	$C_{24}H_{25}BrF_2N_2O_2$	491.1140	491.1121
Ex. 165	piperidin-1-yl	$C_{26}H_{27}BrF_2N_2O_2$	517.1297	517.1341
Ex. 166	(2-hydroxyethyl)amino	$C_{23}H_{23}BrF_2N_2O_3$	493.0933	493.0961
Ex. 167	bis(2-hydroxyethyl)amino	$C_{25}H_{27}BrF_2N_2O_4$	537.1195	537.1171
Ex. 168	piperazin-1-yl	$C_{25}H_{26}BrF_2N_3O_2$	518.1249	518.1280

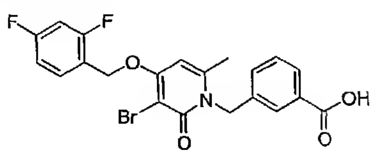
NMR characterization of compounds of Examples 161-168

Ex. No.	NMR Data

Ex. 161	^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (q, J = 7.6 Hz, 1H); 7.42-7.35 (m, 2H), 7.24-7.20 (m, 2H), 7.03 (app t, J = 8.4 Hz, 2H), 6.51 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H); 4.07 (s, 2H); 2.04 (s, 3H)
Ex. 162	^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (app q, J = 7.6 Hz, 1H); 7.26-7.22 (m, 2H), 7.15 (s, 2H), 7.01 (app d, J = 6.4 Hz, 2H), 6.95 (app dt, J = 1.2, 8.0 Hz, 1H); 6.88-6.82 (m, 1H); 5.98 (s, 1H), 5.35 (s, 2H), 5.20 (s, 2H); 3.69 (t, J = 8.4 Hz, 4H); 3.46 (s, 2H); 2.41 (m, 4H); 2.29 (s, 3H)
Ex. 163	^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (app q, J = 7.6 Hz, 1H); 7.25-7.14 (m, 3H); 7.01-6.92 (m, 2H); 6.85 (m, 1H); 5.97 (s, 1H), 5.36 (s, 2H), 5.20 (s, 2H); 3.38 (s, 2H); 2.28 (s, 3H); 2.21 (s, 6H)
Ex. 164	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.25-7.22 (m, 2H); 7.14 (s, 1H), 6.99 (app d, 6.8 Hz, 1H), 6.94 (app dt, J = 2.0, 8.0 Hz, 1H), 6.88-6.80 (m, 1H); 5.97 (s, 1H), 5.34 (s, 2H), 5.19 (s, 2H); 3.73 (s, 2H); 2.28 (s, 3H); 2.82 (app heptet, J = 6.0 Hz, 1H), 1.07 (d, J = 6.0 Hz, 6H)
Ex. 165	^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.27 (app t, J = 8.0 Hz, 1H); 7.20 (app d, J = 7.6 Hz, 1H); 7.08 (bs, 1H); 7.01 (app t, J = 8.0 Hz, 2H); 6.48 (s, 1H), 5.41 (s, 2H), 5.28 (s, 2H); 3.44 (s, 2H); 2.35 (s, 3H); 2.40-2.30 (m, 4H); 1.57-1.53 (m, 4H); 1.48-1.38 (m, 2H)
Ex. 166	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (app q, J = 8.0 Hz, 1H); 7.22-7.14 (m, 3H); 7.09 (bs, 1H); 6.98 (app d, J = 7.2 Hz, 1H); 6.89 (app dt, J = 1.6, 8.0 Hz, 1H); 6.81-6.76 (m, 1H); 5.92 (s, 1H), 5.28 (s, 2H), 5.14 (s, 2H); 3.73 (s, 2H); 3.59 (app t, J = 4.8 Hz, 2H); 2.73 (app t, J = 4.8 Hz, 2H); 2.24 (s, 3H)
Ex. 167	^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.46 (app d, J = 8.8 Hz, 2H); 7.31 (bs, 1H); 7.27 (app t, J = 8.0 Hz, 1H); 7.03 (app t, J = 8.8 Hz, 2H); 6.54 (s, 1H), 5.44 (s, 2H), 5.30 (s, 2H); 4.47 (s, 2H); 3.90-3.84 (m, 4H); 3.40-3.25 (m, 4H); 2.40 (s, 3H)
Ex. 168	^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (app q, J = 8.0 Hz, 1H); 7.53-7.46 (m, 2H); 7.36 (bs, 1H); 7.30 (app d, J = 7.6 Hz, 1H); 7.05-7.01 (m, 2H); 6.55 (s, 1H), 5.44 (s, 2H), 5.30 (s, 2H); 4.47 (s, 2H); 3.58-3.53 (m, 8H); 2.42 (s, 3H)

Example 169

3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid

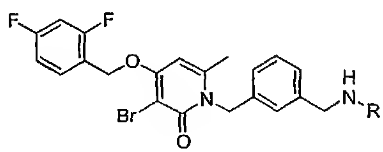


Preparation of 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid. EXAMPLE 154 (150 mg, 0.31 mmol) was dissolved in tetrahydrofuran (5 mL).

Potassium trimethylsilanolate (80 mg, 0.62 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to an oil and purified by reversed phase chromatography (C_{18}, 0.1% aqueous trifluoroacetic acid/acetonitrile) to yield the product (64 mg, 44%) ^1H NMR (400 MHz, CD_3OD) δ 7.92 (*app* d, J = 8.0 Hz, 1H); 7.78 (s, 1H); 7.62 (*app* q, J = 8.0 Hz, 1H); 7.44 (t, J = 7.6 Hz, 1H); 7.36 (*app* d, J = 8.0 Hz, 1H); 7.02 (*app* t, J = 7.6 Hz, 2H); 6.51 (s, 1H), 5.48 (s, 2H), 5.30 (s, 2H); 2.37 (s, 3H). ES HRMS m/z 464.0328 ($C_{21}H_{16}BrF_2NO_4$ requires 464.0304).

Examples 170-174

The compounds of Examples 170-174 are prepared using the compound of Example 159 or 161:



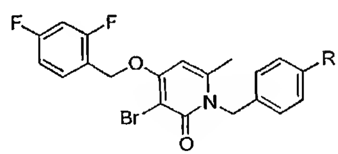
Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 170	-C(O)CH_3	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.0772
Ex. 171	-C(O)OCH_3	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0731
Ex. 172	-SO_2CH_3	$C_{22}H_{21}BrF_2N_2O_4S$	527.0446	527.0430
Ex. 173	-C(O)CH_2OH	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0712
Ex. 174	-C(O)NH_2	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0751

NMR characterization of compounds of Examples 170-174

Ex. No.	NMR Data
Ex. 170	^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (*app* q, *J* = 8.0 Hz, 1H); 7.28 (*app* t, *J* = 8.0, 1H), 7.18 (*app* d, *J* = 8.0 Hz, 1H), 7.05-7.00 (m, 4H); 6.49 (s, 1H), 5.41 (s, 2H), 5.29 (s, 2H); 2.37 (s, 3H); 1.94 (s, 3H)
Ex. 171	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (*app* q, *J* = 7.6 Hz, 1H); 7.25 (*app* t, *J* = 8.0, 1H), 7.17 (*app* d, *J* = 8.0 Hz, 1H), 7.06-7.02 (m, 2H); 6.97-6.91 (m, 1H); 6.87-6.82 (m, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 4.30 (d, *J* = 6.0 Hz, 2H); 3.67 (s, 3H); 2.28 (s, 3H)
Ex. 172	^{1}H NMR (400 MHz, CD_3CN) δ 7.58 (*app* q, *J* = 7.6 Hz, 1H); 7.31 (*app* t, *J* = 8.0, 1H), 7.24 (*app* d, *J* = 8.0 Hz, 1H), 7.11 (s, 1H); 7.05-7.00 (m, 3H); 6.32 (s, 1H), 6.06 (bs, 1H), 5.31 (s, 2H), 5.23 (s, 2H); 4.17 (d, *J* = 6.4 Hz, 2H); 2.78 (s, 3H); 2.28 (s, 3H)
Ex. 173	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (*app* q, *J* = 8.0 Hz, 1H); 7.23 (*app* t, *J* = 7.6, 1H), 7.15 (*app* d, *J* = 7.2 Hz, 1H), 7.05-7.00 (m, 3H); 6.94 (*app* dt, *J* = 1.2, 8.8 Hz, 1H); 6.88-6.81 (m, 1H); 6.03 (s, 1H), 5.27 (s, 2H), 5.19 (s, 2H); 4.39 (d, *J* = 6.4 Hz, 2H); 4.05 (s, 2H), 2.31 (s, 3H)
Ex. 174	^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (*app* q, *J* = 8.0 Hz, 1H); 7.28 (*app* t, *J* = 8.0, 1H), 7.19 (*app* d, *J* = 8.0 Hz, 1H), 7.05-6.96 (m, 4H); 6.49 (s, 1H), 5.41 (s, 2H), 5.29 (s, 2H); 4.25 (s, 2H); 2.35 (s, 3H)

Examples 175-185

The compounds of Examples 175-175 are prepared using the compounds of Examples 159 or 160:



Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 175	$-CH_2NHCH(CH_3)_2$	$C_{24}H_{25}BrF_2N_2O_2$	491.1140	491.1143
Ex. 176	morpholin-4-ylmethyl	$C_{25}H_{25}BrF_2N_2O_3$	519.1089	519.1062
Ex. 177	$-CH_2N(CH_3)_2$	$C_{23}H_{23}BrF_2N_2O_2$	477.0984	477.0931
Ex. 178	piperidin-1-ylmethyl	$C_{26}H_{27}BrF_2N_2O_2$	517.1297	517.1258

Ex. 179	[bis(2-hydroxyethyl)amino]mehtyl	$C_{25}H_{27}BrF_2N_2O_4$	537.1195	537.1181
Ex. 180	$-CH_2NHCH_2CH_2OH$	$C_{23}H_{23}BrF_2N_2O_3$	493.0933	493.0907
Ex. 181	piperazin-1-ylmethyl	$C_{25}H_{26}BrF_2N_3O_2$	518.1249	518.1213
Ex. 182	$-CH_2NHC(O)OCH_3$	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0752
Ex. 183	$-CH_2NHC(O)CH_3$	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.0793
Ex. 184	$-CH_2NHSO_2CH_3$	$C_{22}H_{21}BrF_2N_2O_4S$	527.0446	527.0431
Ex. 185	$-CH_2NHC(O)NH_2$	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0720

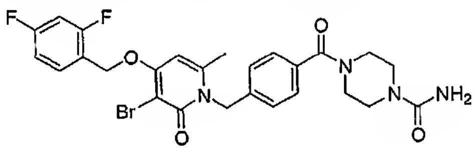
NMR characterization of compounds of Examples 175-185

Ex. No.	NMR Data
Ex. 175	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, *J* = 8.0 Hz, 1H); 7.25 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.94 (*app* t, *J* = 8.0 Hz, 1H), 6.88-6.80 (m, 1H); 5.97 (s, 1H), 5.31 (s, 2H), 5.19 (s, 2H); 3.74 (s, 2H); 2.82 (*app* heptet, *J* = 6.0 Hz, 1H), 2.28 (s, 3H); 1.09 (d, *J* = 6.4 Hz, 6H)
Ex. 176	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, *J* = 8.0 Hz, 1H); 7.25 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.94 (*app* dt, *J* = 2.0, 8.0 Hz, 1H), 6.87-6.81 (m, 1H); 5.97 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 3.67 (*app* t, *J* = 4.8 Hz, 4H); 3.44 (s, 2H); 2.44-2.38 (m, 4H), 2.29 (s, 3H)
Ex. 177	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, *J* = 8.0 Hz, 1H); 7.23 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.93 (*app* dt, *J* = 2.0, 8.0 Hz, 1H), 6.86-6.81 (m, 1H); 5.96 (s, 1H), 5.33 (s, 2H), 5.18 (s, 2H); 3.38 (s, 2H); 2.29 (s, 3H); 2.20 (s, 6H)
Ex. 178	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, *J* = 8.0 Hz, 1H); 7.24-7.20 (m, 2H), 7.10-7.07 (m, 2H), 6.96-6.90 (m,1H), 6.86-6.81 (m, 1H); 5.96 (s, 1H), 5.32 (s, 2H), 5.18 (s, 2H); 3.34 (s, 2H); 2.31 (s, 3H); 2.31-2.28 (m, 4H); 1.53-1.51 (m, 4H); 1.39 (m, 2H)
Ex. 179	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (q, *J* = 8.0 Hz, 1H); 7.25 (d, *J* = 8.0 Hz, 2H); 7.12 (d, *J* = 8.0 Hz, 2H); 6.94 (dt, *J* = 8.8 Hz, 2H); 6.87-6.82 (m, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 3.68 (s, 2H); 3.61 (t, *J* = 5.2 Hz, 4H); 2.70 (t, *J* = 5.2 Hz, 4H); 2.29 (s, 3H)
Ex. 180	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (q, *J* = 8.0 Hz, 1H); 7.25 (d, *J* = 8.0 Hz, 2H); 7.12 (d, *J* = 8.0 Hz, 2H); 6.94 (*app* dt, *J* = 8.8 Hz, 2H); 6.87-6.82 (m, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 3.68 (s, 2H); 3.61 (t, *J* = 5.2 Hz, 4H); 2.70 (t, *J* = 5.2 Hz, 4H); 2.29 (s, 3H)
Ex. 181	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (q, *J* = 8.0 Hz, 1H); 7.52 (d, *J* = 8.0 Hz, 2H); 7.25 (d, *J* = 8.0 Hz, 2H); 7.03 (*app* t, *J* = 8.0 Hz, 2H); 6.53 (s, 1H), 5.44 (s, 2H), 5.30 (s, 2H); 4.32 (bs, 2H); 3.55-3.35 (m, 8H); 2.39 (s, 3H)

Ex. 182	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (*app* q, *J* = 8.0 Hz, 1H); 7.20 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.94 (*app* dt, *J* = 1.2, 8.0 Hz, 1H), 6.87-6.81 (m, 2H); 5.97 (s, 1H), 5.32 (s, 2H), 5.19 (s, 2H); 4.31 (d, *J* = 6.0 Hz, 2H); 3.68 (s, 3H); 2.28 (s, 3H)
Ex. 183	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (*app* q, *J* = 8.0 Hz, 1H); 7.23 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.04-6.99 (m, 2H); 6.47 (s, 1H), 5.39 (s, 2H), 5.28 (s, 2H); 4.30 (s, 2H); 2.34 (s, 3H); 1.95 (s, 3H)
Ex. 184	^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (*app* q, *J* = 8.0 Hz, 1H); 7.34 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.02 (*app* t, *J* = 8.8 Hz, 2H), 6.48 (s, 1H), 5.42 (s, 2H), 5.28 (s, 2H); 4.21 (s, 2H); 2.82 (s, 3H); 2.35 (s, 3H)
Ex. 185	^{1}H NMR (400 MHz, d_7DMF) δ 7.76 (*app* q, *J* = 8.0 Hz, 1H); 7.28 (d, *J* = 8.0 Hz,), 7.14 (d, *J* = 8.0 Hz, 2H), 7.34-7.26 (m, 1H); 7.22-7.14 (m, 1H); 6.62 (s, 1H), 5.65 (s, 2H), 5.39 (s, 2H), 5.37 (s, 2H); 4.26 (d, *J* = 6.0 Hz, 2H); 2.40 (s, 3H)

Example 186

4-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoyl)piperazine-1-carboxamide

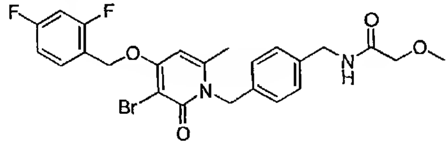


3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one (300 mg, 0.54 mmol) was dissolved in *N,N*-dimethylacetamide (5 mL). Trimethylsilyl isocyanate (0.15 mL, 1.08 mmol) was added followed by *N,N*-diisopropylethylamine (0.23 mL, 1.3 mmol) and the reaction was stirred for 1 hour at ambient temperature. The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1.3 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1.38 mmol/g) were added. The mixture was shaken for 6 hours, filtered, and the resulting filtrate was concentrated to a white solid (279 mg, 90%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (*app* q, *J* = 8.0 Hz, 1H); 7.41 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.03 (*app* t, *J* = 8.8 Hz, 2H); 6.51 (s, 1H), 5.46 (s, 2H), 5.30 (s, 2H), 3.75-3.35 (m, 8H);

2.37 (s, 3H). ES HRMS m/z 575.1104 ($C_{26}H_{25}BrF_2N_4O_4$ requires 575.1100).

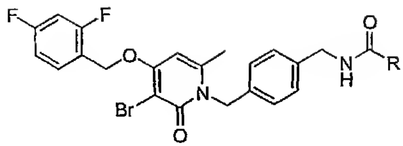
Example 187

N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl}methyl}benzyl)-2-methoxyacetamide



Polymer bound carbodiimide resin (2.3 g, 1.18 meq/g, 2.7 mmol) was suspended in *N,N*-dimethylformamide. Acetoxyacetic acid (120 mg, 1.33 mmol) was added, followed by 1-hydroxybenzotriazole (1M in *N,N*-dimethylformamide, 0.165 mL) and *N,N*-diisopropylethylamine (0.3 mL, 2.0 mmol). The reaction was shaken for 1 hour when EXAMPLE 159 (300 mg, 0.67 mmol) was added. The reaction was shaken for 16 hours and then diluted with tetrahydrofuran. Polyamine resin (1 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (2 g, 1.38 mmol/g) were added and the mixture was shaken for 72 hours, filtered and the resulting filtrate concentrated. Trituration with water followed by trituration with ether yielded a white solid (125 mg, 36%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (*app* q, *J* = 8.0 Hz, 1H); 7.21 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.94 (*app* t, *J* = 8.8 Hz, 1H), 6.88-6.81 (m, 1H); 5.97(s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 4.43 (d, *J* = 6.0 Hz, 2H); 3.92 (s, 2H); 3.39 (s, 3H); 2.29 (s, 3H). ES HRMS m/z 521.0882 ($C_{24}H_{22}BrF_2N_2O_4$ requires 521.0882).

Examples 188-193

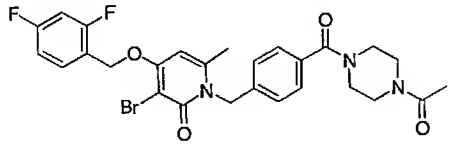


By following the general method for the preparation of Example 187 and substituting the appropriate carboxylic acid for acetoxyacetic acid, the compounds of Examples 188-193 are prepared. These compounds were triturated with water and again with ether and purified by chromatography (silica gel, hexane/ethyl acetate) as appropriate to yield off-white solids. Example 191 was prepared from its *N*-t-butoxycarbonyl protected intermediate. Deprotection was accomplished with 4N HCl in dioxane to afford the title compound as its hydrochloride salt (86 mg, 24%). Deprotection of the methyl ester from Ex. 188 was accomplished with K_2CO_3 in methanol/water to yield Ex. 192 as a white solid. The yields and analytical data are shown below.

Compound No.	R	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 188	CH_2OCOCH_3	49	$C_{25}H_{23}BrF_2N_2O_5$	549.0831	549.0849
Ex. 189	$C(CH_3)_2OH$	13	$C_{25}H_{25}BrF_2N_2O_4$	535.1039	535.1035
Ex. 190	$C(-CH_2CH_2-)OH$	33	$C_{25}H_{23}BrF_2N_2O_4$	535.0865	535.0876
Ex. 191	CH_2NH_2	24	$C_{23}H_{22}BrF_2N_3O_3$	533.0882	533.0899
Ex. 192	CH_2OH	25	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0730
Ex. 193	$CH_2NHCOCH_3$	81	$C_{25}H_{24}BrF_2N_3O_3$	548.0991	548.1000

Example 194

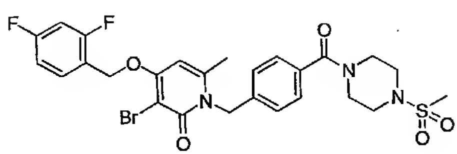
1-{4-[(4-acetylpiperazin-1-yl)carbonyl]benzyl}-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one (200 mg, 0.36 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). *N,N*-Diisopropylethylamine (0.25 mL, 1.44 mmol) was added followed by acetic anhydride (0.10 mL, 1.06 mmol). The reaction was stirred for 2 hours at ambient temperature. and concentrated to an oil that was triturated in ether and again in water to yield an off-white solid (131 mg, 63%) ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (app q, *J* = 8.0 Hz, 1H); 7.42 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.62-7.02 (m, 1H); 7.02 (app t, *J* = 8.0 Hz, 1 H); 6.52 (s, 1H), 5.46 (s, 2H), 5.30 (s, 2H); 3.80-3.65 (m, 8H); 2.37 (s, 3H); 2.11 (s, 3H). ES HRMS m/z 574.1150 ($C_{27}H_{26}BrF_2N_3O_4$ requires 574.1148).

Example 195

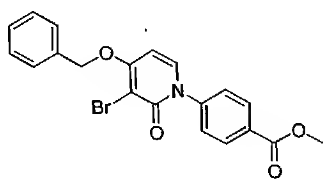
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(4-{[4-(methylsulfonyl)piperazin-1-yl]carbonyl}benzyl)pyridin-2(1H)-one



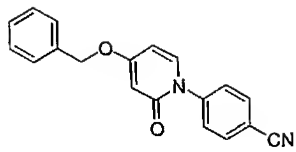
3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1H)-one (300 mg, 0.54 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). 4-Methylmorpholine (0.23 mL, 2.2 mmol) was added followed by methanesulfonyl chloride (0.10 mL, 1.33 mmol) and the reaction was stirred for 2 h. The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1.3 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1.38 mmol/g) were added. The mixture was shaken for 16 hours, filtered, and the resulting filtrate concentrated to an oil that was triturated with water. The resulting white solid was collected, washed with ether and dried (172 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (*app* q, J = 8.2 Hz, 1H); 7.34 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.02 (*app* dt, J = 1.2, 8.8 Hz, 1H), 6.88-6.82 (m, 1H); 6.02 (s, 1H), 5.37 (s, 2H), 5.21 (s, 2H); 3.80-3.20 (m, 8H); 2.79 (s, 3H); 2.30 (s, 3H). ES HRMS m/z 610.0851 ($C_{26}H_{26}BrF_2N_3O_5S$ requires 610.0817).

Example 196

Methyl-4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoate.

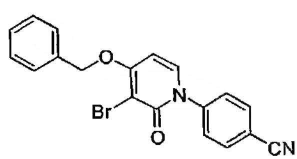


Step 1. Preparation of 4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile.



4-benzyloxy-2(1H)-pyridone (12.00 g, 59.63 mmol) was dissolved in dimethyl sulfoxide (100 mL). Potassium carbonate (10.99 g, 79.50 mmol) was added, followed by 4-fluorobenzonitrile (4.81 g, 39.75 mmol). The reaction was stirred at 100 °C for 18 hours. After cooling to room temperature the reaction was diluted with H_2O (150 mL) and the solids were collected by filtration washing with diethyl ether. Chromatography (silica gel, hexanes/ethyl acetate) provided an off-white solid (7.78 g, 65%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.44-7.41 (m, 5H), 7.22 (d, *J* = 13.3, 1H), 6.13 (dd, *J* = 2.6, 7.7 Hz, 1H), 6.06 (d, *J* = 2.6 Hz, 1H), 5.07 (s, 2H).

Step 2. Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile .



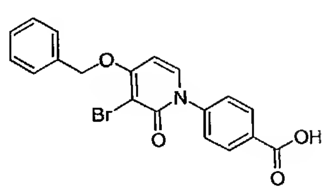
4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile (Step 1) (2.76 g, 9.13 mmol) was suspended in acetonitrile (50 mL) and cooled in an ice-bath. *N*-bromosuccinimide (1.71 g, 9.54 mmol) was added. Once the addition was complete the cooling bath was removed. After stirring for 45 minutes the reaction was diluted with acetonitrile and solids were collected by

filtration to give a white solid (3.13 g, 90%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.5, 2H), 7.50-7.37 (m, 5H), 6.63 (d, J = 7.9 Hz, 1H), 5.41 (s, 2H).

Step 3. Preparation of methyl-4-[4-(benzyl)oxy-3-bromo-2-oxopyridin-1(2H)-yl]benzoate. 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile (Step 2) (1.50 g, 3.93 mmol) suspended in methanol (50 mL) was cooled in an ice-bath. HCl (g) was then bubbled through the mixture for 5 minutes. The reaction was then stirred at room temperature overnight, at which time the reaction mixture was concentrated. The residue was suspended in 6*N* HCl (60 mL) and heated at reflux for 1.5 hours. After cooling to room temperature the solids were collected by filtration. Chromatography (silica gel, hexanes/ethyl acetate) provided an off-white shiny solid (0.540 g, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.47-7.39 (m, 5H), 6.57 (d, J = 7.9 Hz, 1H), 5.38 (s, 2H), 3.86 (s, 3H). ES-HRMS m/z 416.0355 (M+H caldc for $C_{20}H_{16}BrNO_4$ requires 414.0341).

Example 197

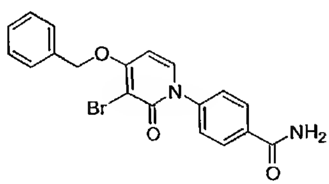
4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoic acid.



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoic acid. EXAMPLE 196 (0.460 g, 1.11 mmol) was dissolved in tetrahydrofuran (5.0 mL). Potassium trimethylsilanolate (0.285 g, 2.22 mmol) was added. The reaction was stirred at room temperature for 3 hours at which time H_2O (10 mL) was added. The aqueous reaction mixture was acidified (pH-3) with 1*N* HCl. The tetrahydrofuran was evaporated, additional H_2O (50 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated to provide a rust colored solid (0.444 g, 100%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.50-7.34 (m, 5H), 6.57 (d, J = 7.9 Hz, 1H), 5.38 (s, 2H). ES-HRMS m/z 400.0191 (M+H calcd for $C_{19}H_{14}BrNO_4$ requires 400.0184).

Example 198

4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzamide.

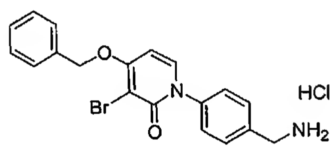


Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzamide. STEP 2, EXAMPLE 196 (0.238 g, 0.624 mmol) was suspended in tert-butyl alcohol (3.0 mL). KF on 40 wt % Al_2O_3 (0.453 g, 3.12 mmol) was added. The reaction mixture was heated at reflux for 5 days. Additional KF on 40 wt % Al_2O_3 (0.453 g, 3.12 mmol) was added and heating was continued at reflux overnight. After cooling to room temperature

chloroform and methanol were added and the solids were collected by filtration. Chromatography (reverse-phase, acetonitrile/H_2O) provided a tan solid (0.073 g, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 7.8 Hz, 1H), 7.47-7.34 (m, 7H), 6.56 (d, J = 7.9 Hz, 1H), 5.38 (s, 2H). ES-HRMS m/z 399.0372 (M+H calcd for $C_{19}H_{15}BrN_2O_3$ requires 399.0344).

Example 199

1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one.

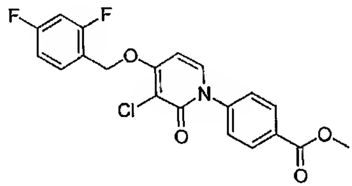


Preparation of 1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one. STEP 2, EXAMPLE 196 (1.25 g, 3.28 mmol) was dissolved in tetrahydrofuran (15 mL). Borane-dimethylsulfide (3.44 mL, 6.89 mmol, 2.0 M in tetrahydrofuran) was added and the mixture heated at reflux. After 14.5 hours the solvent was evaporated. 0.5*M* NaOH (50 mL) was added followed by ethyl acetate. The aqueous layer was neutralized with 1*N* HCl. Methanol saturated with HCl was added and the mixture was heated at reflux for 5 hours. After cooling to room temperature, diethyl ether was added and the solids were collected by filtration. The solids were treated with 4*N* HCl in dixoane (5 mL) and methanol (1 mL) at room temperature for 1 hour, at which time diethyl ether was added and the solids were collected by filtration to give a tan solid (0.920 g,

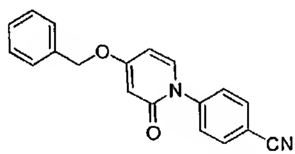
67%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (br s, 2H), 7.76 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.50-7.37 (m, 7H), 6.56 (d, J = 7.6 Hz, 1H), 5.41 (s, 2H), 4.09 (br s, 2H). ES-HRMS m/z 385.0555 (M+H calcd for $C_{19}H_{17}BrN_2O_2$ requires 385.0552).

Example 200

Methyl-4-[3-chloro-4-[(2,4-diflurobenzyl)oxy]-2-oxypyridin-1(2H)-yl]benzoate.



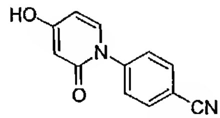
Step 1. Preparation of 4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile.



4-benzyloxy-2(1H)-pyridone (50.0 g, 248.47 mmol) was dissolved in dimethyl sulfoxide (300 mL). Potassium carbonate (68.68 g, 496.94 mmol) was added, followed by 4-fluorobenzonitrile (31.60 g, 260.89 mmol). The reaction was stirred at 100 °C for 20 hours. After cooling to room temperature the reaction was diluted with H_2O (600 mL) and the solids were collected by filtration washing with diethyl ether. The solids were then washed with hot methanol to provide a tan solid (55.6 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.54 (d, J

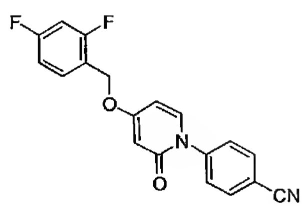
= 8.5 Hz, 2H), 7.44-7.41 (m, 5H), 7.22 (d, *J* = 13.3, 1H), 6.13 (dd, *J* = 2.6, 7.7 Hz, 1H), 6.06 (d, *J* = 2.6 Hz, 1H), 5.07 (s, 2H).

Step 2. Preparation of 1-[4-nitrilephenyl]-4-hydroxy-2(1H)-pyridinone.



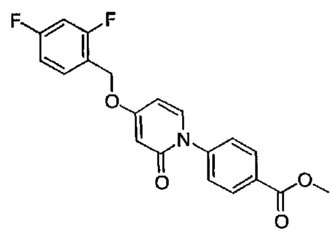
4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile (Step 1) (20.0 g, 66.15 mmol) was dissolved in methanol (300 mL). Ammonium formate (8.34 g, 132.3 mmol) was added followed by 5% Pd/C (6.62 g). The resulting mixture was heated at reflux for 20 minutes at which time the reaction began to exotherm. The reaction was allowed to cool to room temperature at which time it was filtered through a pad of Celite® washing with methanol. The filtrate was evaporated to provide a pale yellow solid (16.2 g, >100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7,95 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 5.98 (dd, *J* = 2.6, 7.7 Hz, 1H), 5.54 (d, *J* = 2.4 Hz, 1H).

Step 3. Preparation of 4-[4-[(2,4-difluorobenzyloxy)]-2-oxopyridin-1(2H)-yl]benzonitrile.



1-[4-Nitrilephenyl]-4-hydroxy-2(1H)-pyridinone (Step 2) (16.2 g) was dissolved in *N,N*-dimethylformamide (100 mL). Potassium carbonate (10.06 g, 72.77 mmol) was added followed by α-bromo-2,4-difluorotoluene (8.91 mL, 69.46 mmol). The resulting mixture was heated to 65°C for 1 hour. Additional α-bromo-2,4-difluorotoluene (4.25 mL, 33.08 mmol) was added. The resulting mixture was heated to 65°C for 5 hours. Additional α-bromo-2,4-difluorotoluene (2.12 mL, 16.54 mmol) was added. After stirring at 65°C overnight the reaction was allowed to cool to room temperature. H_2O (300 mL) was added and the solid was collected by filtration. A portion (8.0 g) of the solids were washed with hot methanol to give a pale yellow solid (6.22 g, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.72-7.64 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.40-7.32 (m, 1H), 7.22-7.16 (m, 1H), 6.17-6.11 (m, 2H), 5.17 (s, 2H).

Step 4. Preparation of methyl-4-[4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]benzoate.



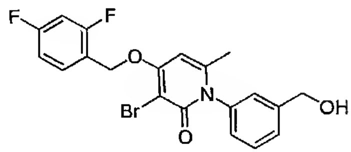
4-[4-[(2,4-difluorobenzyloxy)]-2-oxopyridin-1(2H)-yl]benzonitrile (Step 3) (2.00 g, 5.91 mmol) suspended in methanol (20 mL) and H_2O (5 mL) was cooled in an ice-bath. HCl (g) was bubbled through the mixture until most of the solids dissolved. The resulting mixture was then heated at reflux for 3 hours. The reaction was then recooled in an ice-bath

and HCl was bubbled through the mixture for 5 minutes. The mixture was heated at reflux for 2 hours and then the methanol was evaporated. Additional H_2O (50 mL) was added and the aqueous reaction mixture was extracted with ethyl acetate (50 mL) and tetrahydrofuran (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) gave an off-white solid (0.630 g, 29%). ^{1}H NMR (300 MHz, DMF-d_6) δ 8.15 (d, J = 8.5 Hz, 2H), 7.80 (*app* q, J = 7.9 Hz, 1H), 7.74-7.67 (m, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.42-7.34 (*app* dt, J = 2.4, 9.0 Hz, 1H), 7.28-7.22 (m, 1H), 6.20 (dd, J = 2.6, 7.6 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 5.28 (s, 2H), 3.98 (s, 3H).

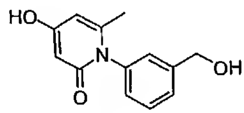
Step 5. Preparation of methyl-4-[3-chloro-4-[(2,4-diflurobenzyl)oxy]-2-oxypyridin-1(2H)-yl]benzoate. Methyl-4-[4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]benzoate (Step 4) (0.520 g, 1.40 mmol) was suspended in acetonitrile (10.0 mL). *N*-chlorosuccinimide (0.196 g, 1.47 mmol) was added followed by several drops of dichloroacetic acid. The resulting mixture was heated at reflux overnight. After cooling to room temperature additional acetonitrile was added and the precipitate was collected by filtration to give an off-white solid (0.331 g, 58%). ^{1}H NMR (300 MHz, DMF-d_6) δ 8.34 (d, J = 8.5 Hz, 2H), 8.12 (d, J = 7.9 Hz, 1H), 8.04-7.96 (m, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.59-7.53 (m, 1H), 7.52-7.41 (m, 1H), 7.05 (d, J = 7.9 Hz, 1H), 5.70 (s, 2H), 4.15 (s, 3H). ES-HRMS m/z 406.0644 (M+H calcd for $C_{20}H_{14}ClF_2NO_4$ requires 406.0652).

Example 201

3-Bromo-4-[(2,4-diflurorbenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one.

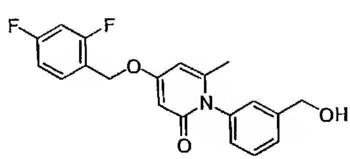


Step 1. Preparation of 4-Hydroxy-1-[3-(hydroxymethyl)phenyl]6-methylpyridin-2(1H)-one.



4-hydroxy-6-methyl-2-pyrone (10.0 g, 79.3 mmol) and 3-aminobenzyl alcohol (9.77g, 79.3 mmol) were combined in H_2O (100 mL) and heat at reflux. After 48 hours at reflux the reaction mixture was concentrated. The residue was treated with methanol and the precipitate was collected by filtration to give a pale yellow solid (3.04 g, 17%). ^{1}H NMR (300 MHz, DMSO-d_6) d 10.6 (br s, 1H), 7.46-7.35 (m, 2H), 7.09-7.03 (m, 2H), 5.88 (d, J = 1.6 Hz, 1H), 5.55 (d, J = 2.6 Hz, 1H), 4.54 (d, J = 4.2 Hz, 2H), 1.83 (s, 3H).

Step 2. Preparation of 1-[3-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.

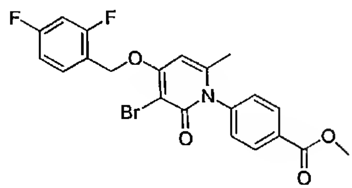


4-Hydroxy-1-[3-(hydroxymethyl)phenyl]6-methylpyridin-2(1H)-one (Step 1) (0.674 g, 2.91 mmol) was suspended in acetone (10 mL). Cesium carbonate (1.04 g, 3.21 mmol) was added followed by α-bromo-2,4-difluorotoluene (0.392 mL, 3.06 mmol). After stirring at room temperature for 2 days the reaction was concentrated. The residue was portioned between H_2O (30 mL) and ethyl acetate (30 mL). The aqueous layer was further extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. Chromatography (on silica, hexanes/ethyl acetate with 10% methanol) provided a white solid (0.531 g, 51%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.51-7.39 (m, 3H), 7.82 (s, 1H), 7.16 (d, *J* = 26.8 Hz, 1H), 7.08-6.86 (m, 2H), 6.00 (d, *J* = 2.6 Hz, 1H), 5.92 (d, *J* = 2.6 Hz, 1H), 5.05 (s, 2H), 4.68 (s, 2H), 1.93 (s, 3H). ES-HRMS m/z 358.1256 (M+H calcd for $C_{20}H_{17}F_2NO_3$ requires 358.1249).

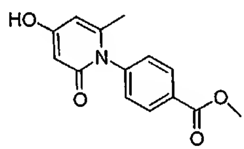
Step 3. Preparation of 3-bromo-4-[(2,4-diflurorbenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one . 1-[3-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Step 2) (0.460 g, 1.29 mmol) was suspended in acetonitrile (5.0 mL) and cooled in an ice-bath. *N*-bromosuccinimide (0.241 g, 1.35 mmol) was added. Once the addition was complete the cooling bath was removed. After stirring for 1.5 hours the reaction was diluted with acetonitrile and solids were collected by filtration to give a white solid (0.385 g, 68%). ^1H NMR (300 MHz, DMSO-d_6) d 7.70 (app q, J = 7.9 Hz, 1H), 7.49-7.32 (m, 3H), 7.24-7.10 (m, 3H), 6.66 (s, 1H), 5.35 (s, 2H), 4.56 (d, J = 5.6 Hz, 2H), 1.95 (s, 3H). ES-HRMS m/z 436.0384 (M+H calcd for $C_{20}H_{16}BrF_2NO_3$ requires 436.0354).

Example 202

Methyl-4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.



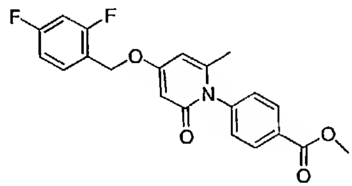
Step 1. Preparation of Methyl 4-(4-hydroxy-6-methyl-2-oxypyridin-1(2H)-yl)benzoate.



4-hydroxy-6-methyl-2-pyrone (21.00 g, 166.70 mmol) and 4-methylaminobenzoate (25.20 g, 166.70 mmol) were combined in 1,2-dichlorobenzene (50 mL) and rapidly heated to 160 °C. After 15 minutes at 160 °C the reaction was allowed to cool to room temperature. The reaction was diluted with dichloromethane (50 mL) and extracted with saturated Na_2CO_3 (2 x 100 mL). The combined aqueous layers were acidified (pH-2) with concentrated HCl. The precipitate was collected by filtration and washed with diethyl ether to give a yellow/orange solid (10.9 g, 25%). ^1H NMR (300 MHz, DMSO-d_6) δ 10.8 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz,

2H), 5.95 (d, J = 2.4 Hz, 1H), 5.61 (d, J = 2.4, 1H), 3.91 (s, 3H), 1.85 (s, 3H).

Step 2. Preparation of Methyl-4-[4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.



Methyl 4-(4-hydroxy-6-methyl-2-oxypyridin-1(2H)-yl)benzoate (Step 1) (10.90 g, 42.04 mmol) was dissolved in *N,N*-dimethylformamide (100 mL). Potassium carbonate (6.97 g, 50.45 mmol) was added, followed by 2,4-difluorobenzyl bromide (5.66 mL, 44.14 mmol). The reaction was stirred at room temperature for 3 days then diluted with H_2O (100 mL). The reaction mixture was extracted into ethyl acetate and tetrahydrofuran (2 x 100 mL). The precipitate was collected by filtration and the organic filtrate was washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. The resulting solid was combined with the precipitate to provide a pale pink solid (6.77 g, 42%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (d, J = 8.3 Hz, 2H), 7.67 (q, J = 7.9 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.35 (m, 1H), 7.18 (*app* dt, J = 1.6, 8.5 Hz, 1H), 6.08 (d, J = 1.8 Hz, 1H), 5.98 (d, J = 2.4 Hz, 1H), 5.14 (s, 2H), 3.91 (s, 3H), 1.87 (s, 3H).

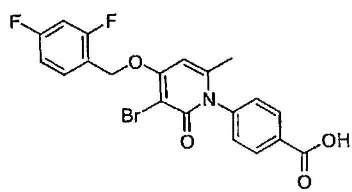
Step 3. Preparation of methyl-4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.

Methyl-4-[4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-

yl]benzoate (Step 2) (6.74 g, 17.49 mmol) suspended in acetonitrile (100 mL) was cooled in an ice-bath. *N*-bromosuccinimide (3.27 g, 18.36 mmol) was added. After 1 hour the ice-bath was removed and after an additional 30 minutes the reaction was diluted with acetonitrile (20 mL). The precipitate was collected by filtration to provide the title compound as an off-white solid (6.94 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 2H), 7.61 (q, J = 7.9 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.02-6.96 (m, 1H), 6.90 (app dt, J = 2.4, 9.5 Hz, 1H), 6.14 (s, 1H), 5.28 (s, 2H), 3.98 (s, 3H), 2.00 (s, 3H). ES-HRMS m/z 464.0304 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464.0301).

Example 203

4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid.

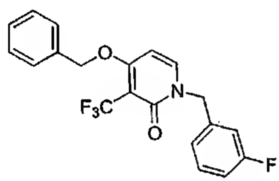


EXAMPLE 202 (7.43 g, 16.00 mmol) was dissolved in tetrahydrofuran (40 mL). Potassium trimethylsilanolate (4.10 g, 32.00 mmol) was added and the reaction mixture was stirred at room temperature for 22 hours. The tetrahydrofuran was evaporated and H_2O (50 mL) was added. The aqueous reaction mixture was acidified with 1*N* HCl and the precipitate was collected by filtration. The solids were washed with boiling methanol to give an off-white solid (5.05 g, 70%). ^{1}H NMR

(300 MHz, DMSO-d_6) δ 13,2 (br s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.72 (q, J = 7.9 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.38 (app dt, J = 2.4, 9.9 Hz, 1H), 7.23 (app dt, J = 1.8, 8.5 Hz, 1H), 6.72 (s, 1H), 5.37 (s, 2H), 1.97 (s, 3H). ES-HRMS m/z 450.0154 (M+H calcd for $C_{20}H_{14}BrF_2NO_4$ requires 450.0147).

Example 204

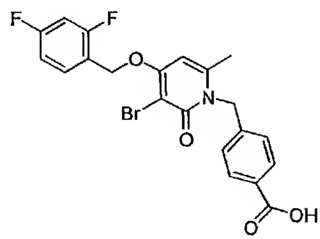
4-(Benzyloxy)-1-(3-fluorobenzyl)-3-(trifluoromethyl)pyridin-2(1H)-one.



The starting material (0.250 g, 0.591 mmol) was dissolved in 1-methyl-2-pyrrolidinone (5.0 mL). Trifluoroacetic acid, sodium salt (0.322 g, 2.36 mmol) was added, followed by copper(I)iodide (0.225 g, 1.18 mmol). The resulting mixture was heated to 180°C for 5 hours and then allowed to cool to room temperature. The reaction was diluted with H_2O (50 mL) and brine (50 mL), then extracted into ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Chromatography (reverse-phase, acetonitrile/H_2O) provided an off-white solid (0.050 g, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 8H), 7.06 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 6.07 (d, J = 7.7 Hz, 1H), 5.20 (s, 2H), 5.06 (s, 2H). ES-HRMS m/z 378.1097 (M+H calcd for $C_{20}H_{15}F_4NO_2$ requires 378.1112).

Example 205

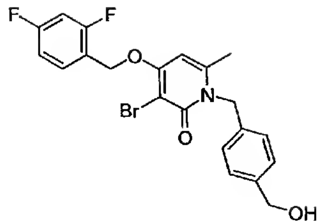
4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid



EXAMPLE 153 (50.0 g, 104.54 mmol) was dissolved in methanol (500 mL) and dioxane (100 mL). 1*N* NaOH (130 mL, 130 mmol) was added. The resulting mixture was heated to 50 °C for 5.5 hours. The reaction was partially concentrated and the heterogenous mixture was acidified (pH 2) with 1*N* HCl. The precipitate was collected by filtration to afford a white solid (49.2 g, >100 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 8.3 Hz, 2H), 7.70 (*app* q, J = 7.9 Hz, 1H), 7.35 (dt, J = 2.2, 9.9 Hz, 1H), 7.18 (*app* d, J = 8.3 Hz, 2H), 7.17-7.12 (m, 1H), 6.64 (s, 1H), 5.41 (s, 2H), 5.33 (s, 2H), 2.32 (s, 3H). ES-HRMS m/z 464.0327 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464.0304).

Example 206

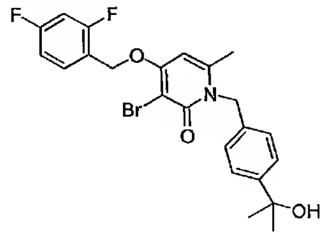
3-Bromo-4-[(2,4-diflurobenzyl)oxy]-1-[4-(hydroxymethyl)benzyl]-6-methylpyridin-2(1H)-one.



Example 205 (40.0 g, 86.16 mmol) suspended in tetrahydrofuran (300 mL) was cooled in an ice-bath. Borane dimethylsulfide (129.2 mL, 258.48 mmol, 2.0 *M* in tetrahydrofuran) was slowly added. The resulting mixture was slowly allowed to warm to room temperature overnight. The mixture was recooled in an ice-bath and quenched by the addition of small pieces of ice. After the evolution of gas ceased additional ice-water was added. The flask was fitted with a distillation apparatus and the dimethylsulfide was removed. After the reaction was cooled to room temperature, H_2O (300 mL), ethyl acetate (200 mL) and tetrahydrofuran (300 mL) were added. The precipitate that formed was collected by filtration and the filtrate was placed in a separatory funnel. The aqueous layer was further extracted with ethyl acetate (300 mL). The combined organic layers were washed with brine (300 mL). The organic phase was dried over Na_2SO_4 and evaporated which was combined with the precipitate to yield an off-white solid (37.8 g, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (*app* q, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.86 (*app* dt, *J* = 2.3, 8.6 Hz, 1H), 6.79 (*app* dt, *J* = 2.4, 8.4 Hz, 1H), 6.00 (s, 1H), 5.28 (s, 2H), 5.16 (s, 2H), 4.57 (s, 2H), 2.25 (s, 3H). ES-HRMS m/z 450.0512 (M+H calcd for $C_{21}H_{18}BrF_2NO_3$ requires 450.0511).

Example 207

3-Bromo-4-[(2,4-diflurobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)benzyl]-6-methylpyridin-2(1H)-one.

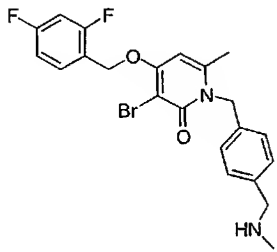


Preparation of 3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)benzyl]-6-methylpyridin-2(1H)-one. EXAMPLE 153 (2.00 g, 4.18 mmol) suspended in tetrahydrofuran (20 mL) was cooled in the dry ice/acetone bath. Methyl magnesium bromide (4.32 mL, 12.96 mmol, 3.0 *M* in diethyl ether) was slowly added. The reaction was slowly allowed to warm to room temperature overnight. The reaction was then cooled in an ice bath and quenched by the addition of saturated NH_4Cl (50 mL). H_2O was added and the reaction was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filerted and evaporated. The residue was subjected to chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) to provide an off-white foam. The foam was dissolved in acetonitrile and cooled in an ice bath. *N*-bromosuccinimide (0.057 g, 0.320 mmol) was added. Once the addition was complete the cooling bath was removed. After 2.5 hours at room temperature the reaction was concentrated. Purification by chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (*app* q, J = 7.7 Hz, 1H), 7.39 (d, J = 78.3 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 6.92 (*app* dt, J = 1.7, 8.4 Hz, 1H), 6.86-6.81 (m, 1H), 5.97 (s, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 2.29

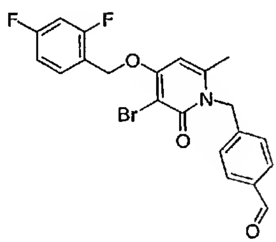
(s, 3H), 1.52 (s, 6H). ES-HRMS m/z 478.0811 (M+H $C_{23}H_{22}BrF_2NO_3$ requires 478.0824).

Example 208

3-bromo-4-[(2,4-diflurobenzyl)oxy]- 6-methyl-1-{4-[(methylamino)methyl]benzyl}pyridin-2(1H)-one.



Step 1. Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzaldehyde.



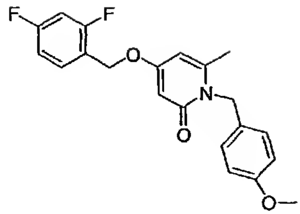
EXAMPLE 206 (1.30 g, 2.89 mmol) was suspended in acetonitrile (10 mL) and cooled in an ice-bath. 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole 1-oxide (0.580 g, 1.44 mmol) was added and the reaction mixture was stirred at room temperature overnight. Diethyl ether was added and the solid was collected by filtration to give a white solid (1.14 g,

88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.56 (*app* q, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.93 (*app* dt, *J* = 1.6, 8.3 Hz, 1H), 6.87-6.82 (m, 1H), 6.02 (s, 1H), 5.41 (s, 2H), 5.20 (s, 2H), 2.27 (s, 3H).

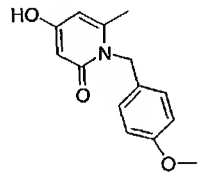
Step 2. 3-bromo-4-[(2,4-diflurobenzyl)oxy]- 6-methyl-1-{4-[(methylamino)methyl]benzyl}pyridin-2(1H)-one. 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzaldehyde (Step 1) (1.53 g, 3.41 mmol) of step 1 was dissolved in *N,N*-dimethylformamie (5.0 mL). Methylamine (3.41 mL, 6.83 mmol, 2.0 M in tetrahydrofuran) was added followed by $NaHB(OAc)_3$ (2.17 g, 10.23 mmol) in *N,N*-dimethylformamide (8.0 mL) and acetic acid (2.0 mL). The reaction was stirred at room temperature overnight at which time 1N NaOH (50 mL) was added and then extracted with ethyl acetate (2 x 50 mL). The organic layers were washed with brine (25 mL), dried over Na_2SO4 and evaporated. Chromatography (on silica, ethyl acetate with 5% methanolic ammonia/hexanes) afforded a tan solid (0.810 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (*app* q, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.92 (*app* dt, *J* = 2.4, 8.3 Hz, 1H), 6.90-6.80 (m, 1H), 5.95 (s, 1H), 5.32 (s, 2H), 5.17 (s, 2H), 3.68 (s, 2H), 2.40 (s, 3H), 2.27 (s, 3H). ES-HRMS m/z 463.0838 (M+H calcd for $C_{22}H_{21}BrF_2N_2O_4$ requires 463.0827).

Example 209

4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2-(1H)-one.



Step 1. Preparation of 1-(4-methoxybenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one.



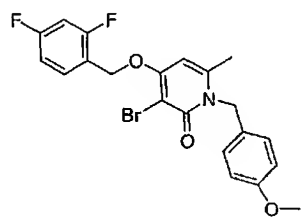
4-Hydroxy-6-methyl-2-pyrone (4.60 g, 36.45 mmol) and 4-methoxybenzylamine (5.00 g, 36.45 mmol) in H_2O (100 mL) were heated to reflux. After 15 hours at reflux the reaction was allowed to cool to room temperature. The precipitate was collected by filtration washing with H_2O to give a pale yellow solid (8.00 g, 89 %). ^1H NMR (400 MHz, DMSO-d_6) δ 7.2 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.74 (d, J = 2.0 Hz, 1H), 5.56 (d, J = 2.5 Hz, 1H), 5.08 (s, 2H), 3.68 (s, 3H), 2.14 (s, 3H).

Step 2. Preparation of 4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one. 1-(4-methoxybenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (Step 1) (7.97 g, 32.49 mmol) was dissolved in *N,N*-dimethylformamide (60 mL). Potassium carbonate (4.94 g, 35.74 mmol) was added, followed by α-bromo-2,4-difluorotoluene (4.38 mL, 34.11 mmol). The reaction was stirred at room temperature for 20 hours at which time the mixture was filtered through a pad of Celite®

washing with acetonitrile and the filtrate was evaporated. The residue was dissolved in H_2O (150 mL) and extracted into ethyl acetate (2 x 100 mL). The organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated. Chromatography (on silica, hexanes/ethyl acetate with 10% methanol) yielded an off-white solid (3.64 g, 30%). ^1H NMR (300 MHz $CDCl_3$) δ 7.42 (*app* q, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.96-6.84 (m 2H), 6.85 (*app* d, *J* = 8.7 Hz, 2H), 6.01 (d, *J* = 2.6 Hz, 1H), 5.82 (d, *J* = 2.8 Hz, 1H), 5.23 (s, 2H), 5.02 (s, 2H), 3.79 (s, 3H), 2.25 (s, 3H). ES-HRMS m/z 372.1412 (M+H $C_{21}H_{19}F_2NO_3$ requires 372.1417).

Example 210

3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one

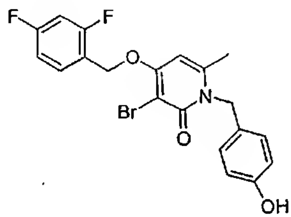


Preparation of 3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one. EXAMPLE 209 (0.200 g, 0.538 mmol) suspended in acetonitrile (3 mL) was cooled in an ice-bath. *N*-bromosuccinimide (0.101 g, 0.565 mmol) was added. Once the addition was complete the cooling bath was removed. After 1 hour the reaction was concentrated. Purification by chromatography (silica gel, hexanes/ethyl acetate) provided a white solid (0.240 g, 99%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (*app* q, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.97 (app dt, *J* = 2.4, 8.6 Hz, 1H), 6.91-6.83 (m,

1H), 6.85 (*app* d, J = 8.7 Hz, 2H), 5.98 (s, 1H), 5.31 (s, 2H), 5.21 (s, 2H), 3.79 (s, 3H), 2.34 (s, 3H). ES-HRMS m/z 450.0491 (M+H $C_{21}H_{18}BrF_2NO_3$ requires 450.0511).

Example 211

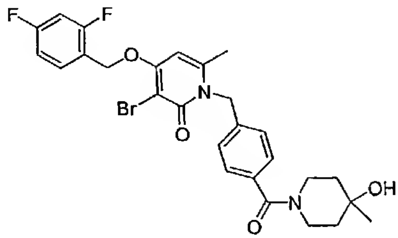
3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-hydroxybenzyl)-6-methylpyridin-2(1H)-one



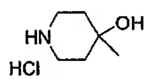
Preparation of 3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-hydroxybenzyl)-6-methylpyridin-2(1H)-one. EXAMPLE 210 (0.235 g, 0.522 mmol) was suspended in acetonitrile (3 mL). Cerric ammonium nitrate (1.14 g, 2.09 mmol) dissolved in H_2O (1 mL) was added. The reaction was stirred at room temperature for 1 hour and then diluted with dichloromethane (25 mL). The reaction was then washed with H_2O (10 mL). The aqueous phase was back extracted with dichloromethane (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was washed with hot ethyl acetate to give an off-white solid (0.134 g, 59%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (*app* q, J = 7.9 Hz, 1H), 7.65 (s, 1H), 7.45-7.36 (m, 1H), 7.36 (d, J = 10.1Hz, 2H), 7.27-7.20 (m, 1H), 6.49 (d, J = 10.1 Hz, 2H), 5.60 (s, 2H), 5.07 (s, 2H), 2.63 (s, 3H). ES-HRMS m/z 436.0187 (M+H $C_{20}H_{16}BrF_2NO_3$ requires 436.0354).

Example 212

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one.



Step 1. Preparation of 4-hydroxy-4-methylpiperidine hydrochloride.

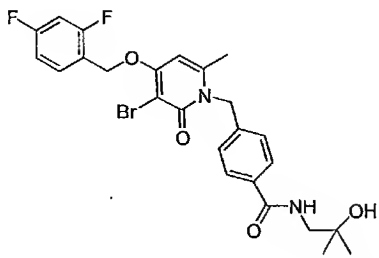


tert-Butyl-4-oxo-1-piperidine (10.0 g, 50.19 mmol) dissolved in diethyl ether (100 mL) was cooled in an ice-bath. Methyl magnesium bromide (18.40 mL, 55.21 mmol, 3.0 *M* in diethyl ether) was added. After slowly warming to room temperature the reaction was recooled in an ice-bath and quenched by the addition of saturated NH_4Cl (75 mL). Additional H_2O was added and the organic layer was removed. The aqueous layer was further extracted with diethyl ether (50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography (silica gel, hexanes/ethyl acetate) provided a clear oil. The resulting oil was dissolved in diethyl ether (10 mL) and treated with 4*N* HCl/dioxane (32.61 mL, 130.43 mmol). After stirring at room temperature for 1 hour the reaction mixture was concentrated to give a pale yellow solid (5.05 g, >100%).

Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one. THE ACID (0.300 g, 0.646 mmol) was suspended in dichloromethane (6.0 mL). 1-hydroxybenzotriazole (0.044 g, 0.323 mmol) was added followed by 3-(1-cyclohexylcarbodiimide)propyl-functionalized silica gel (2.02 g, 1.29 mmol, loading = 0.64 mmol/g), 3-(1-morpholine)propyl functionalized silica gel (1.84 g, 1.29 mmol, loading = 0.7 mmol/g) and dichloromethane (2 mL). After stirring at room temperature for 15 minutes, 4-hydroxy-4-methylpiperidine hydrochloride (0.147 g, 0.969 mmol) was added. The resulting mixture was stirred at room temperature overnight, at which time dimethylamine-3-functionalized silica gel (1.7 g, 2.58 mmol, loading = 1.5 mmol/g) was added followed by isocyanate-3-functionalized silica gel (1.3 g, 1.62 mmol, loading = 1.22 mmol/g). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was then filtered and concentrated. Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam (0.200 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (*app* q, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.96 (*app* t, *J* = 8.3 Hz, 1H), 6.87 (*app* dt, *J* = 2.0, 9.5 Hz, 1H), 6.06 (s, 1H), 5.38 (s, 2H), 5.22 (s, 2H), 4.27 (*br* m, 1H), 3.41 (*br* m, 3H), 2.30 (s, 3H), 2.06 (s, 1H), 1.60 (*br* m, 4H), 1.28 (s, 3H). ES-HRMS m/z 561.1173 (M+H $C_{27}H_{27}BrF_2N_2O_4$ requires 561.1195).

Example 213

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]- 6-methyl-2-oxypyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide.

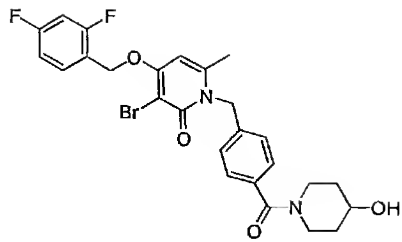


The title compound was by a procedure essentially as in Example 212 using 1-amino-2-methyl-2-propanol hydrochloride as starting material.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.53 (*app* q, J = 7.8 Hz, 1H), 7.33 (t, J = 5.8 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 6.95-6.90 (m, 1H), 6.86-6.81 (m, 1H), 6.04 (s, 1H), 5.30 (s, 2H), 5.19 (s, 2H), 3.40 (d, J = 5.9 Hz, 2H), 2.98 (*br* s, 1H), 2.24 (s, 3H), 1.21 (s, 6H). ES-HRMS m/z 535.1012 (M+H $C_{25}H_{25}BrF_2N_2O_4$ requires 535.1039).

Example 214

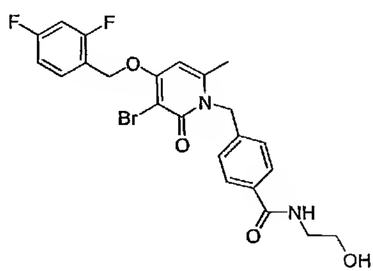
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxypiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one.



The title compound was produced essentially as in Example 212 using 4-hydroxypiperidine as starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (*app* q, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.94 (*app* dt, *J* = 2.4, 8.4 Hz, 1H), 6.84 (*app* ddd, *J* = 2.6, 8.9, 10.3 Hz, 1H), 6.01 (s, 1H), 5.36 (s, 2H), 5.19 (s, 2H), 4.12-4.07 (m, 1H), 3.96-3.90 (m, 1H), 3.60 (*br* s, 1H), 3.33 (*br* s, 1H), 3.13 (*br* s, 1H), 2.27 (s, 3H), 1.91 (*br* s, 3H), 1.77 (*br* s, 1H), 1.57 (*br* s, 1H), 1.44 (*br* s, 1H). ES-HRMS m/z 547.1006 (M+H $C_{26}H_{25}BrF_2N_2O_4$ requires 547.1039).

Example 215

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzamide.

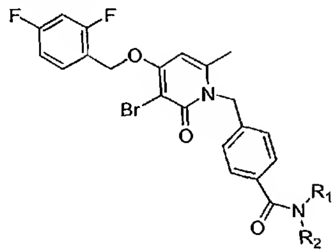


Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-*N*-(2-hydroxyethyl)benzamide. To a reaction vessel (borosilicate culture tube) was added EXAMPLE 205 (0.300 g, 0.646 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added to the reaction vessel followed by approximately 1.10 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. Ethanolamine (0.06 mL, 0.994 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.6 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed further with tetrahydrofuran (2 x 10 mL) and combined with the partially reduced filtrate. The resulting filtrate was concentrated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid. (0.111 g, 34%) ^1H NMR (400 MHz, DMF-d_6) δ 8.45 (t, *J* = 5.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.76 (*app* q, *J* = 7.9 Hz, 1H), 7.33-7.27 (m, 1H), 7.27 (*app* d, *J* = 7.9 Hz, 2H), 7.20 (*app* dt, *J* = 2.4, 8.6 Hz, 1H), 6.65 (s, 1H), 5.47 (s, 2H), 5.38 (s, 2H), 4.83 (*br* s, 1H),

3.64-3.60 (m, 2H), 2.47-3.42 (m, 2H), 2.40 (s, 3H). ES-HRMS m/z 507.0742 (M+H $C_{23}H_{21}BrF_2N_2O_4$ requires 507.0726).

Example 216-231

Preparation of 3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(aminocarbonyl)benzyl]pyridin-2(1H)-one compounds



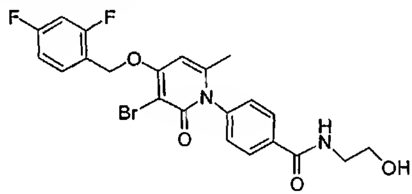
By following the method of Example 215 and substituting the appropriate amine, the compounds of Examples 216-231 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R_1	R_2	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 216	CH_2CH_2NH-	CH_2CH_2NH-	73	$C_{25}H_{24}BrF_2N_3O_4$	532.1042	532.102
Ex. 217	H	$CH_2CH_2NH_2$	49	$C_{23}H_{22}BrF_2N_3O_3$	506.0885	506.088
Ex. 218	H	$CH_2CH_2CH_2NH_2$	31	$C_{24}H_{24}BrF_2N_3O_3$	520.1042	520.104
Ex. 219	H	OH	53	$C_{21}H_{17}BrF_2N_2O_4$	479.0413	479.042
Ex. 220	H	CH_3	59	$C_{22}H_{19}BrF_2N_2O_4$	477.0620	477.060
Ex. 221	CH_3	CH_3	51	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.079
Ex. 222	CH_2CH_2O-	CH_2CH_2O-	61	$C_{25}H_{23}BrF_2N_2O_4$	533.0882	533.090
Ex. 223	CH_2CH_2OH	CH_2CH_2OH	69	$C_{25}H_{25}BrF_2N_2O_5$	551.0988	551.097
Ex. 224	$CH_2CH_2CH_2$-	$CH_2CH_2CH_2$-	66	$C_{26}H_{25}BrF_2N_2O_3$	531.1084	531.108
Ex. 225	H	$CH(CH_3)_2$	50	$C_{24}H_{23}BrF_2N_2O_3$	505.0933	505.090

Ex. 226	CH_2CH_2-	CH_2CH_2-	71	$C_{25}H_{23}BrF_2N_2O_3$	517.0933	517.0908
Ex. 227	$CH_2CH_2N(CH_3)$-	$CH_2CH_2N(CH_3)$-	83	$C_{26}H_{26}BrF_2N_3O_3$	546.1198	546.1215
Ex. 228	H	$CH_2CH_2N(CH_3)_2$	81	$C_{25}H_{26}BrF_2N_3O_3$	534.1198	534.1197
Ex. 229	H	$CH_2CH_2OCH_3$	79	$C_{24}H_{23}BrF_2N_2O_4$	521.0882	521.0861
Ex. 230	CH_3	CH_2CH_2OH	36	$C_{24}H_{23}BrF_2N_2O_4$	521.0882	521.0893
Ex. 231	CH_3	$CH_2CH_2OCH_3$	82	$C_{25}H_{25}BrF_2N_2O_4$	535.1039	535.1028

Example 232

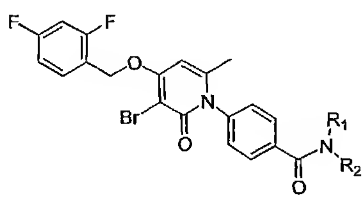
4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]- N-(2-hydroxyethyl)benzamide.



Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]- N-(2-hydroxyethyl)benzamide. To a reaction vessel (borosilicate culture tube) was added EXAMPLE 203 (0.300 g, 0.666 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added to the reaction vessel followed by approximately 1.13 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. Ethanolamine (0.06 mL, 0.994 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated

with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.7 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed further with tetrahydrofuran (2 x 10 mL) and combined with the partially reduced filtrate. The resulting filtrate was concentrated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor). Purification by chromatography (silica gel) provided an off-white solid (0.155 g, 47%). ^{1}H NMR (400 MHz, DMF-d_6) δ 8.58 (t, J = 5.5 Hz, 1H), 8.10 (d, J = 8.3 Hz, 2H), 7.79 (*app* q, J = 7.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.36-7.30 (m, 1H), 7.21 (*app* dt, J = 2.4, 8.5 Hz, 1H), 6.73 (s, 1H), 5.43 (s, 2H), 3.68 (*app* t, J = 5.9 Hz, 2H), 3.52-3.49 (m, 2H), 2.03 (s, 3H). ES-HRMS m/z 493.0597 (M+H $C_{22}H_{19}BrF_2N_2O_4$ requires 493.0569).

Examples 233-243

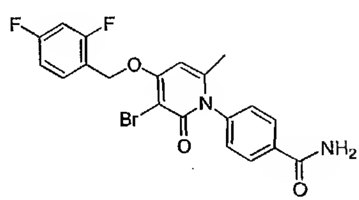


By following the method of Example 232 and substituting ethanolamine for the appropriate amine, the compounds of Examples 233-243 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R_1	R_2	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 233	CH_2CH_2NH-	CH_2CH_2NH-	40.3	$C_{24}H_{22}BrF_2N_3O_3$	518.0885	518.0866
Ex. 234	H	$CH_2CH_2NH_2$	57.1	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0748
Ex. 235	H	$CH_2CH_2CH_2NH_2$	21.5	$C_{23}H_{22}BrF_2N_3O_3$	506.0885	506.0915
Ex. 236	H	OH	33.9	$C_{20}H_{15}BrF_2N_2O_4$	465.0256	465.0259
Ex. 237	H	CH_3	20.7	$C_{21}H_{17}BrF_2N_2O_3$	463.0463	463.0479
Ex. 238	CH_3	CH_3	22.3	$C_{22}H_{19}BrF_2N_2O_3$	477.0620	477.0643
Ex. 239	CH_2CH_2O-	CH_2CH_2O-	84.4	$C_{24}H_{21}BrF_2N_2O_4$	519.0726	519.0723
Ex. 240	CH_2CH_2OH	CH_2CH_2OH	46.6	$C_{24}H_{23}BrF_2N_2O_5$	537.0831	537.0854
Ex. 241	$CH_2CH_2CH_2$-	$CH_2CH_2CH_2$-	76.5	$C_{25}H_{23}BrF_2N_2O_3$	517.0933	517.0892
Ex. 242	H	$CH(CH_3)_2$	52.6	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.0781
Ex. 243	CH_2CH_2-	CH_2CH_2-	47.2	$C_{24}H_{21}BrF_2N_2O_4$	503.0776	503.0791

Ex. 244

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide.

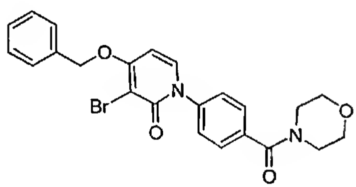


Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide. EXAMPLE 203 (0.500 g, 1.11 mmol) was suspended in tetrahydrofuran (5.0 mL). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0.234 g, 1.33 mmol) was added followed by 4-methylmorpholine (0.366 mL, 3.33 mmol). The resulting mixture was stirred at room temperature for 1.5

hours at which time NH_4OH (2.5 mL) was added. The resulting mixture was stirred at room temperature overnight. H_2O (25 mL) and tetrahydrofuran (25 mL) was added. The aqueous layer was further extracted with ethyl acetate (25 mL). The combined organic layers were washed with saturated sodium carbonate solution (25 mL), 1*N* HCl (25 mL), brine (25 mL), dried over Na_2SO4, filtered and concentrated to provide a pale yellow solid (0.500 g, 100 %). ^{1}H NMR (400 MHz, DMF-d_6) δ 8.13 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.70 (*app* q, J = 7.9 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.41-7.34 (m, 1H), 7.22 (*app* dt, J = 1.8, 8.5 Hz, 1H), 6.71 (s, 1H), 5.37 (s, 2H), 1.97 (s, 3H). ES-HRMS m/z 449.0281 (M+H $C_{20}H_{15}BrF_2N_2O_3$ requires 449.0307).

Ex. 245

4-(Benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1H)-one.



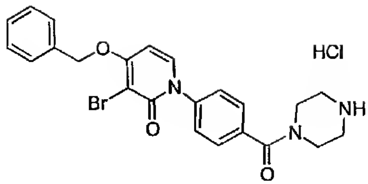
Preparation of 4-(Benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1H)-one. To a reaction vessel (borosilicate culture tube) was added EXAMPLE 197 (0.100 g, 0.250 mmol) which was dissolved in *N,N*-dimethylformamide (2.0 mL). 1-Hydroxybenzotriazole (0.017 g, 0.125 mmol) was added to the reaction vessel followed by approximately 0.423 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction

vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. Morpholine (0.033 g, 0.0.375 mmol) dissolved in *N,N*-dimethlyformamide (0.5 mL) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with *N,N*-dimethylformamide (2.0 mL) and dichloromethane (4.0 mL) and treated with approximately 0.770 g of polyamine resin (2.63 mmol/g) and approximately 1.0 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0.092 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.48-7.33 (m, 7H), 7.27 (d, *J* = 7.8 Hz, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 2H), 3.76-3.47 (*br* m, 8H). ES-HRMS m/z 469.0733 (M+H $C_{23}H_{21}BrN_2O_4$ requires 469.0757).

Ex. 246

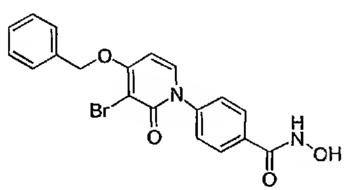
4-(Benzyloxy)-3-bromo-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1H)-one hydrochloride.



Preparation of 4-(benzyloxy)-3-bromo-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1H)-one hydrochloride. By following the method of Ex. 245 and substituting *N*-*tert*-butyl carboxylate piperazine (0.070 g, 0.375 mmol) for morpholine the title compound was prepared as the *N*-t-butoxycarbonyl protected compound. The deprotection of the N-t-butoxycarbonyl intermediate was accomplished with 4*N* HCl in dioxane to afford the title compound as its hydrochloride salt (0.112 g, >100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (*br* s, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.48-7.33 (m, 7H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.38 (s, 2H), 3.79-3.36 (*br* m, 4H), 3.30-3.14 (*br* s, 4H). ES-HRMS m/z 468.0940 (M+H $C_{23}H_{22}BrN_3O_3$ requires 468.0917).

Ex. 247

4-[4-(Benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]-N-hydoxybenzamide.

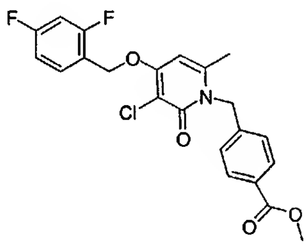


Preparation of 4-[4-(Benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]-N-hydoxybenzamide. By following the method of EXAMPLE 245

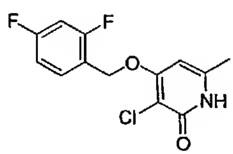
and substituting O-(tetrahydro-2H-pyranyl-2yl) hydroxylamine (0.044 g, 0.375 mmol) for morpholine the title compound was prepared as the tetrahydropyranly protected compound. The deprotection of the tetrahydropyranly intermediate was accomplished with 4*N* HCl in dioxane to afford the title compound (0.056 g, >71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (*br* s,1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.48-7.35 (m, 7H), 6.55 (d, *J* = 7.8 Hz, 1H), 5.37 (s, 2H). ES-HRMS m/z 415.0278 (M+H $C_{19}H_{15}BrN_2O_4$ requires 415.0288).

Ex. 248

Methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate.



Step 1. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpridin-2(1H)-one .

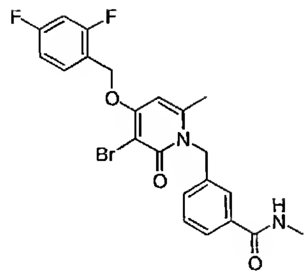


(5.00 g, 19.90 mmol) was suspended in 1,2-dichloroethane (100 mL). Dichloroacetic acid (0.082 mL, 0.995 mmol) was added, followed by *N*-chlorosuccinimide (3.19 g, 23..88 mmol). The reaction mixture was heated at 80 °C for 15.5 hours. The 1,2-

dichloroethane was evaporated and the remaining solids were washed with acetonitrile to provide a tan solid (4.97 g, 88%).

Step 2. Preparation of methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate. 3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpridin-2(1H)-one (Step 1) (4.97 g, 17.40 mmol) suspended in tetrahydrofuran (50 mL) was cooled in an ice-bath. Methyl 4-(bromomethyl)benzoate (5.98 g, 26.10 mmol) was added, followed by sodium hydride (0.835 g, 20.88 mmol, 60% dispersion in mineral oil). Once the addition was complete the cooling bath was removed in the mixture was heated to 50 °C for 19 hours. After cooling to room temperature saturated NH_4Cl (50 mL) was added. Ethyl acetate was added and the precipitate was collected by filtration. The filtrate was further extracted with ethyl acetate. The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. The resulting solid was combined with the precipitate and washed with hot ethyl acetate to give an off-white solid (5.24 g, 69%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.5 Hz, 2H), 7.63 (app q, J = 7.9 Hz, 1H), 7.31 (app dt, J = 2.4, 9.9 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.17-7.13 (m, 1H), 6.60 (s, 1H), 5.36 (s, 2H), 5.27 (s, 2H), 3.81 (s, 3H), 2.27 (s, 3H). ES-HRMS m/z 434.0931 (M+H $C_{22}H_{18}BrF_2NO_4$ requires 434.0965).

Example 249

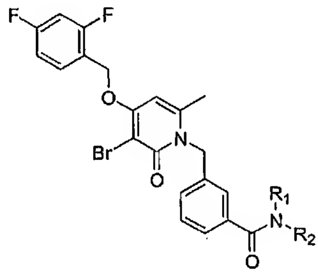


3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-*N*-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 169 (0.300 g, 0.646 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added followed by approximately 1.10 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. *N*-Methylamine (0.50 mL, 0.999 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (35 mL) and treated with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.6 g of methylisocyanate functionalized polystyrene (1.50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The

filtrate was evaporated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor). Chromatography (C-18, acetonitrile/H_2O with 0.1% trifluoroacetic acid) afforded a white solid (0.178 g, 58%). ^1H NMR (400 MHz, DMF-d_6) δ 7.65-7.53 (m, 3H), 7.37-7.28 (m, 2H), 6.97-6.82 (m, 2H), 6.00 (s, 1H), 5.36 (s, 2H), 5.19 (s, 3H), 2.96 (t, J = 4.83 Hz, 3H), 2.29 (s, 3H). ES-HRMS m/z 477.0635 (M+H $C_{22}H_{19}BrF_2N_2O_3$ requires 477.0620).

Preparation of Examples 250- 261

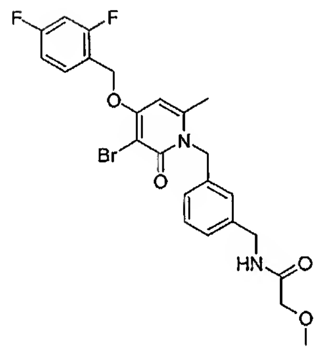


By following the method of Example 249 and replacing N-methylamine with the appropriate amine, the compounds of Examples 250-261 are prepared. The deprotection of the protected intermediates was accomplished with 4N HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R_1	R_2	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 250	CH_2CH_2NH-	CH_2CH_2NH-	89	$C_{25}H_{24}BrF_2N_3O_4$	532.1042	532.1067
Ex. 251	H	$CH_2CH_2NH_2$	75	$C_{23}H_{22}BrF_2N_3O_3$	506.0885	506.0900
Ex. 252	H	$CH_2CH_2CH_2NH_2$	84	$C_{24}H_{24}BrF_2N_3O_3$	520.1042	520.1000
Ex. 253	H	OH	45	$C_{21}H_{17}BrF_2N_2O_4$	479.0413	479.0394
Ex. 254	CH_3	CH_3	69	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.0731

Ex. 255	H	CH_3	58	$C_{22}H_{19}BrF_2N_2O_3$	479.0602	479.0598
Ex. 256	CH_2CH_2O-	CH_2CH_2O-	69	$C_{25}H_{23}BrF_2N_2O_4$	533.0882	533.0857
Ex. 257	H	CH_2CH_2OH	51	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0698
Ex. 258	CH_2CH_2OH	CH_2CH_2OH	25	$C_{25}H_{25}BrF_2N_2O_5$	551.0988	551.0972
Ex. 259	$CH_2CH_2CH_2$-	$CH_2CH_2CH_2$-	62	$C_{26}H_{25}BrF_2N_2O_3$	531.1089	531.1088
Ex. 260	H	$CH(CH_3)_2$	46	$C_{24}H_{23}BrF_2N_2O_3$	505.0933	505.0918
Ex. 261	CH_2CH_2-	CH_2CH_2-	60	$C_{25}H_{23}BrF_2N_2O_3$	517.0933	517.0950

Example 262

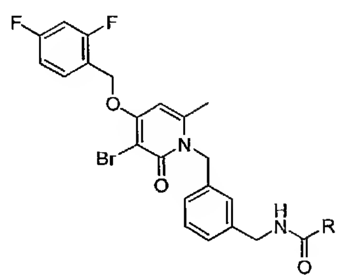


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-methoxyacetamide

To a reaction vessel (borosilicate culture tube) was added methoxyacetic acid (0.09 g, 1.00 mmol). A stock solution of 1-hydroxybenzotriazole (3 mL, 0.16 M) and *N*-methylmorpholine (3 mL, 0.43 M) in *N,N*-dimethylformamide were added to the reaction vessel followed by approximately 0.97 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional *N,N*-dimethylformamide (3 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 4 hours. 1-[3-

(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (0.30 g, 0.668 mmol) was then added to the reaction vessel followed by additional *N,N*-dimethylformamide (5.0 mL) and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.06 g of polyamine resin (2.63 mmol/g) and approximately 2.67 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) afforded a tan solid (0.321 g, 89.4%). ^{1}H NMR (400 MHz, DMF-d_6) δ 8.33 (br s, 1H), 7.81 (*app* q, *J* = 7.85 Hz, 1H), 7.40-7.23 (m, 5H), 7.09 (d, *J* = 7.25 Hz, 1H), 6.68 (s, 1H), 5.46 (s, 2H), 5.42 (s, 2H), 4.45 (d, *J* = 6.24 Hz, 2H), 3.93 (s, 2H), 3.39 (s, 3H), 2.44 (s, 3H). ES-HRMS *m/z* 521.0891 (M+H $C_{24}H_{23}BrF_2N_2O_4$ requires 521.0882).

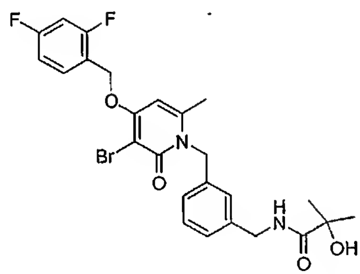
Preparation of Example 263-265



By following the method of Example 262 and replacing methoxyacetic acid with the appropriate acid, the compounds of Examples 263-265 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS *m/z*
Ex. 263	CH_2NH_2	46.1	$C_{23}H_{23}BrF_2N_3O_3$	506.0885	506.0870
Ex. 264	$CH_2NHCOCH_3$	70.4	$C_{25}H_{24}BrF_2N_3O_4$	548.0991	548.1007
Ex. 265	CH_2OCOCH_3	42.7	$C_{23}H_{21}BrF_2N_2O_4$	549.0831	549.0837

Example 266

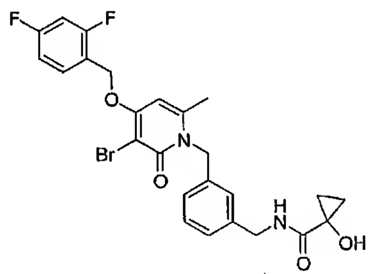


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-hydroxy-2-methylpropanamide

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (0.300 g, 0.668 mmol), 1-hydroxyisobutyric acid (0.215 g, 2.064 mmol), 1-hydroxybenzotriazole (0.112 g, 0.826 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.185 g, 0.963 mmol) were dissolved in *N,N*-dimethylacetamide (3 mL).

N-methylmorpholine (0.209 g, 2.064 mmol) was added, and the reaction stirred for 1 hour at room temperature. The reaction was diluted with H_2O (50 mL) and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organics were then washed with 1*N* HCl (25 mL), saturated Na_2CO_3 (25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated to yield an off-white solid (0.235 g, 64%). ^1H NMR (400 MHz, DMF-d_6) δ 8.25 (br s, 1H), 7.81 (*app* q, *J* = 7.92 Hz, 1H), 7.40-7.21 (m, 5H), 7.09 (d, *J* = 6.84 Hz, 1H), 6.67 (s, 1H), 5.46 (s, 2H), 5.42 (s, 2H), 4.42 (d, *J* = 6.24 Hz, 2H), 2.44 (s, 3H), 1.38 (s, 6H). ES-HRMS *m/z* 535.1024 (M+H $C_{25}H_{25}BrF_2N_2O_4$ requires 535.1039).

Example 267

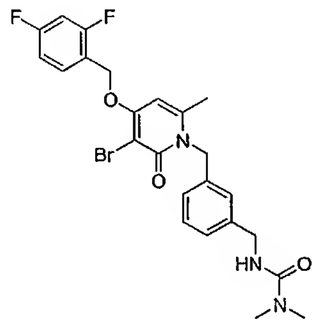


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide

By following the method of Example 266 and substituting 1-hydroxy-1-cyclopropane-carboxylic acid for 1-hydroxyisobutyric acid, the title compound was prepared (0.352 g, 96%). ^1H NMR (400 MHz, DMF-d_6) δ 8.46 (*app* t, *J* = 6.24 Hz, 1H), 7.81 (*app* q,

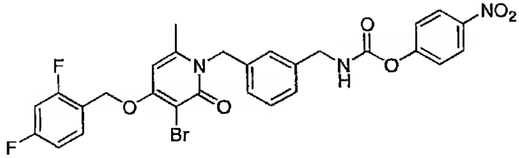
J = 7.92 Hz, 1H), 7.40-7.22 (m, 5H), 7.06 (d, J = 7.05 Hz, 1H), 6.67 (s, 1H), 5.45 (s, 2H), 5.42 (s, 2H), 4.46 (d, J = 6.44 Hz, 2H), 2.45 (s, 3H), 1.17-1.12 (m, 2H), 0.93 (*app* q, J = 3.82 Hz, 2H). ES-HRMS *m/z* 533.0861 (M+H $C_{25}H_{23}BrF_2N_2O_4$ requires 533.0882).

Example 267



N'-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea

Step 1: Preparation of 4-nitrophenyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzylcarbamate .



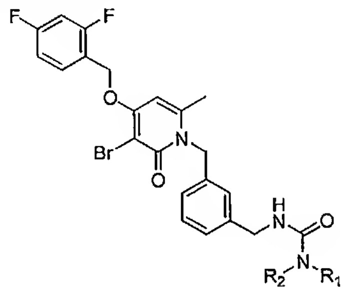
1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (2.00 g, 4.45 mmol)

was suspended in dichloromethane (15 mL). Pyridine was added (0.43 mL, 5.34 mmol). After stirring for 10 minutes at room temperature, a stock solution of 4-nitrophenyl chloroformate (10.0 mL, 0.50 M) in dichloromethane was added dropwise. After stirring for 4.5 hours at room temperature, a stock solution of 4-nitrophenyl chloroformate (2.5 mL, 0.50 M) in dichloromethane was again added dropwise and stirring continued at 40 °C overnight. The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a yellow solid (1.11 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (*app* t, *J* = 6.10 Hz, 1H), 8.24-8.21 (m, 2H), 7.62 (*app* q, *J* = 7.88 Hz, 1H), 7.40-7.27 (m, 7H), 6.98 (d, *J* = 7.52 Hz, 1H), 6.54 (s, 1H), 5.30 (s, 2H), 5.24 (s, 2H), 4.25 (d, *J* = 6.18 Hz, 2H), 2.30 (s, 3H). ES-HRMS *m/z* 614.0753 (M+H $C_{28}H_{22}BrF_2N_3O_6$ requires 614.0733).

Step 2: Preparation of N'-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea . To a reaction vessel (borosilicate culture tube) was added 4-nitrophenyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzylcarbamate (from step 1) (0.350 g, 0.570 mmol) dissolved in dichloromethane (6.0 mL). The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. A stock solution of *N,N*-dimethylamine in tetrahydorfuran (0.427 mL, 2.0 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off

white solid (0.226 g, 63.3%). ^1H NMR (400 MHz, DMF-d_6) δ 7.81 (*app* q, *J* = 7.92 Hz, 1H), 7.40-7.19 (m, 5H), 7.06 (d, *J* = 7.45 Hz, 1H), 6.88 (*app* t, *J* = 5.84 Hz, 1H), 6.68 (s, 1H), 5.45 (s, 2H), 5.42 (s, 1H), 4.35 (d, *J* = 5.84 Hz, 1H), 2.92 (s, 6H), 2.44 (s, 3H). ES-HRMS *m/z* 520.1065 (M+H $C_{24}H_{24}BrF_2N_3O_3$ requires 520.1042).

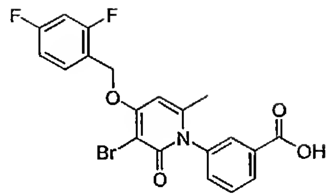
Preparation of Example 268-270



By following the method of Example 267 and replacing *N,N*-dimethylamine with the appropriate amine, the compounds of Examples 268-270 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts.

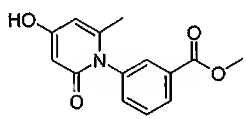
Compound No.	R_1	R_2	% Yield	MF	M+H Requires	ES-HRMS *m/z*
Ex. 268	CH_2CH_2N-	CH_2CH_2N-	66.6	$C_{26}H_{27}BrF_2N_4O_3$	561.1307	561.1309
Ex. 269	H	CH_3	27.0	$C_{23}H_{22}BrF_2N_3O_3$	506.0885	506.0898
Ex. 270	CH_2CH_2O-	CH_2CH_2O-	64.4	$C_{26}H_{26}BrF_2N_3O_4$	562.1148	562.1137

Example 271



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid.

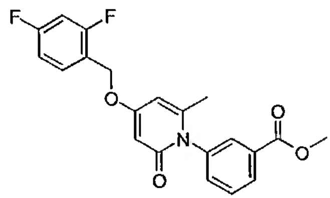
Step 1: Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate .



Methyl 3-aminobenzoate (75.00 g, 496.13 mmol) and 4-hydroxy-6-methyl-2-pyrone (62.57 g, 496.13 mmol) were suspended in 1,2-dichlorobenzene (150 mL) and heated to 165 °C for 15 minutes. The reaction was cooled to room temperature and extracted with 0.54M K_2CO_3 (4 x 250 mL). The aqueous layers were acidified (pH 2) with 4*N* HCl. The precipitate was collected by filtration to afford a yellow-orange solid (20.24 g, 16%). The resulting filtrate was extracted with ethyl acetate (3 x 1 L). The organic layers were washed with brine (500 mL), dried over $MgSO_4$ and evaporated. The resulting solid was washed with hot H_2O to afford a yellow-orange solid (3.84 g, 3%). The two solids were then combined. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (dt, *J* = 1.31, 7.79 Hz, 1H), 7.69 (*app* t, *J* = 1.78 Hz, 1H), 7.62 (t, *J* = 7.78 Hz, 1H) 7.49 (ddd, *J* = 1.07, 1.07, 7.85 Hz, 1H), 5.89 (dd, *J* = 0.87, 2.48 Hz, 1H), 5.55 (*app* d, *J* = 0.94

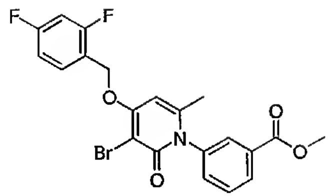
Hz, 1H), 3.83 (s, 3H), 1.80 (s, 3H). ES-HRMS *m/z* 260.0895 (M+H $C_{14}H_{13}NO_4$ requires 260.0917).

Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (from step 1) (24.00 g, 92.57 mmol) and K_2CO_3 (15.35 g, 111.08 mmol) were dissolved in *N,N*-dimethylformamide (220 mL). 2,4-Difluorobenzyl bromide (20.12 g, 97.20 mmol) was then added and the reaction mixture stirred for 48 hours at room temperature. The reaction mixture was diluted with H_2O (1 L) and the precipitate collected by filtration to afford a white solid (4.08 g, 11%). The resulting oil was purified by chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford an off white solid (11.88 g, 33%). The two solids were combined. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dt, *J* = 1.41, 7.79 Hz, 1H), 7.87 (*app* t, *J* = 1.78 Hz, 1H), 7.58 (*app* t, *J* = 7.69 Hz, 1H) 7.45-7.38 (m, 2H), 6.94-6.84 (m, 2H), 5.97 (d, *J* = 2.68 Hz, 1H), 5.90 (ddd, *J* = 0.94, 1.74, 1.74 Hz, 1H), 5.97 (s, 1H), 3.90 (s, 3H), 1.89 (s, 3H). ES-HRMS *m/z* 386.1179 (M+H $C_{21}H_{17}F_2NO_4$ requires 386.1198).

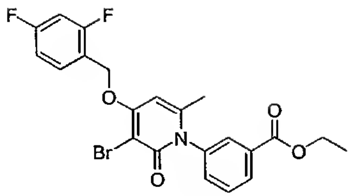
Step 3: Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 2) (15.85 g, 41.130 mmol) suspended in acetonitrile (165 mL) was cooled in an ice-bath. *N*-bromosuccinimide (7.687 g, 43.186 mmol) was added and the ice-bath was removed. The reaction mixture was stirred for 1.5 hours at room temperature. Reaction was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off white solid (17.63 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dt, J = 1.41, 7.85 Hz, 1H), 7.90 (t, J = 1.81 Hz, 1H), 7.67-7.41 (m, 3H), 7.05-6.88 (m, 2H), 6.13 (s, 1H), 5.30 (s, 2H), 3.95 (s, 1H), 2.01 (s, 3H). ES-HRMS m/z 464.0286 (M+H $C_{21}H_{16}BrF_2NO_4$ requires 464.0304).

Step 4: Preparation of the title compound . Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 3) (10.0 g, 21.539 mmol) was dissolved in methanol (36 mL) and tetrahydrofuran (14 mL). 4*N* NaOH (13.5 mL, 53.847 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. The reaction was acidified (pH 2) with 4*N* HCl. The precipitate was collected by filtration to afford an off white solid (7.83 g, 81%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (dt, J = 1.41, 7.65 Hz, 1H), 7.76 (*app* t, J = 1.78 Hz, 1H), 7.76-7.15 (m, 5H), 6.66 (s, 1H), 5.32 (s, 2H), 1.92 (s, 3H). ES-HRMS m/z 450.0134 (M+H $C_{20}H_{14}BrF_2NO_4$ requires 450.0147).

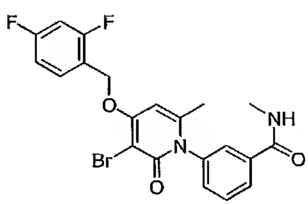
Example 272



Ethyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

By following the method of Example 271 and substituting ethyl 3-aminobenzoate for methyl 3-aminobenzoate, the title compound was prepared (2.66 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dt, *J* = 1.41, 7.85 Hz, 1H), 7.84 (t, *J* = 1.88 Hz, 1H), 7.62-7.55 (m, 2H), 7.36 (*app* dq, *J* = 1.07, 7.85 Hz, 1H), 6.96 (*app* dt, *J* = 2.55, 8.35 Hz, 1H), 6.88-6.84 (m, 1H), 6.08 (s, 1H), 5.25 (s, 2H), 4.42-4.30 (m, 2H), 1.96 (s, 3H), 1.36 (t, *J* = 7.12 Hz, 3H). ES-HRMS *m/z* 478.0482 (M+H $C_{22}H_{18}BrF_2NO_4$ requires 478.0460).

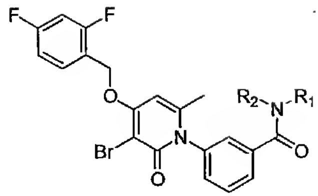
Example 273



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-*N*-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 271 (0.300 g, 0.666 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added to the reaction vessel followed by approximately 0.97 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. *N*-Methylamine in tetrahydrofuran (0.50 mL, 0.999 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (30 mL) and treated with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 3.6 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0.189 g, 61%). ^{1}H NMR (400 MHz, DMF-d_6) δ 8.56 (br d, *J* = 4.16 Hz, 1H), 8.05-7.76 (m, 3H), 7.66 (t, *J* = 7.79 Hz, 1H), 7.56-7.19 (m, 3H), 6.74 (s, 1H), 5.43 (s, 2H), 3.46 (s, 3H), 2.03 (s, 3H). ES-HRMS *m/z* 463.0476 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463.0463).

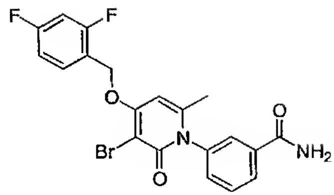
Preparation of Example 274-289



By following the method of Example 273 and replacing *N*-methylamine with the appropriate amine, the compounds of Examples 274-289 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as their hydrochloride salts.

Compound No.	R1	R2	% Yield	MF	M+H Requires	ES-HRMS *m/z*
Ex. 274	CH2CH2NH-	CH2CH2NH-	92.8	$C_{24}H_{22}BrF_2N_3O_3$	518.0885	518.0865
Ex. 275	H	CH2CH2NH2	95.7	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0711
Ex. 276	H	CH2CH2CH2NH2	97.8	$C_{23}H_{22}BrF_2N_3O_3$	506.0885	506.0889
Ex. 277	H	OH	91.0	$C_{20}H_{15}BrF_2N_2O_4$	465.0256	465.0278
Ex. 278	CH3	CH3	67.7	$C_{22}H_{19}BrF_2N_2O_3$	477.0620	477.0626
Ex. 279	CH2CH2O-	CH2CH2O-	86.7	$C_{24}H_{21}BrF_2N_2O_4$	519.0726	519.0696
Ex. 280	H	CH2CH2OH	78.3	$C_{22}H_{19}BrF_2N_2O_4$	493.0569	493.0575
Ex. 281	CH2CH2CH2-	CH2CH2CH2-	87.9	$C_{25}H_{23}BrF_2N_2O_3$	517.0933	517.0918
Ex. 282	H	CH(CH3)2	80.6	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.0797
Ex. 283	CH2CH2-	CH2CH2-	87.9	$C_{24}H_{21}BrF_2N_2O_4$	503.0776	503.0732
Ex. 284	CH2CH2N(CH3)-	CH2CH2N(CH3)-	75.8	$C_{25}H_{24}BrF_2N_3O_3$	532.1042	532.1038
Ex. 285	H	CH2CH2N(CH3)2	86.1	$C_{24}H_{24}BrF_2N_3O_3$	520.1042	520.1030
Ex. 286	H	CH2CH2OCH3	90.2	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0680
Ex. 287	CH3	CH2CH2N(CH3)2	60.0	$C_{25}H_{26}BrF_2N_3O_3$	534.1198	534.1155
Ex. 288	CH3	CH2CH2OH	81.6	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0694
Ex. 289	CH3	CH2CH2OCH3	94.4	$C_{24}H_{23}BrF_2N_2O_4$	521.0882	521.0862

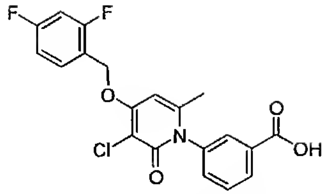
Example 290



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide

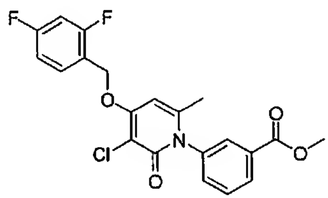
EXAMPLE 271 (2.00 g, 4.44 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.94 g, 5.33 mmol) were suspended in tetrahydrofuran (20 mL). 4-Methylmorpholine (1.5 mL, 13.32 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. NH_4OH (10 mL, 148.00 mmol) was added and the reaction was stirred for 0.5 hours at room temperature. H_2O (50 mL) and tetrahydrofuran (50 mL) were added and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (75 mL) and the combined organics were washed with saturated Na_2CO_3 (50 mL), 1*N* HCl (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated. The resulting solid was washed with diethyl ether to give a white solid (1.86 g, 93%). ^1H NMR (400 MHz, DMF-d_6) δ 8.20 (br s, 1H), 8.10-8.07 (m, 1H), 7.79 (s, 1H), 7.79 (*app* q, *J* = 7.83 Hz, 1H), 7.66 (*app* t, *J* = 7.79 Hz, 1H), 7.57-7.54 (m, 1H), 7.46 (br s, 1H), 7.36-7.19 (m, 2H), 6.74 (s, 1H), 5.43 (s, 2H), 2.04 (s, 3H). ES-HRMS *m/z* 449.0307 (M+H $C_{20}H_{15}BrF_2N_2O_3$ requires 449.0307).

Example 291



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid

Step 1: Preparation of methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

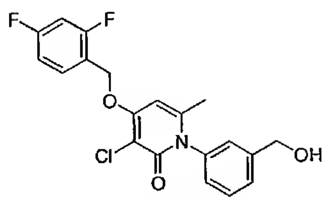


The product from step 2, Example 271 (4.54 g, 11.78 mmol) and *N*-chlorosuccinimide (1.65 g, 12.37 mmol) were suspended in dichloromethane (12 mL). Dichloroacetic acid (0.10 ml, 1.22 mmol) was added and the reaction mixture was stirred overnight at 40 °C. The reaction was cooled to room temperature and a precipitate formed. The precipitate was collected by filtration and washed with dichloromethane (3 x 10 mL) to afford a white solid (1.75 g, 35%). The filtrate was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afforded an off white solid (1.29 g, 26%). The two solids were then combined. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 1.38, 7.83 Hz, 1H), 7.85 (t, *J* = 1.74 Hz, 1H), 7.60-7.52 (m, 2H), 7.37 (dq, *J* =

0.92, 7.92 Hz, 2H), 6.95 (*app* dt, J = 2.55, 8.32 Hz, 1H), 6.89-6.83 (m, 1H), 6.11 (s, 1H), 5.24 (s, 2H), 3.90 (s, 3H), 1.96 (s, 3H). ES-HRMS m/z 420.0783 (M+H $C_{21}H_{16}ClF_2NO_4$ requires 420.0809).

Step 2: Methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 1) (2.90 g, 6.91 mmol) was dissolved in methanol (5 mL) and tetrahydrofuran (12 mL). 4*N* NaOH (4.3 mL, 17.27 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. The reaction was acidified (pH-2) with 4*N* HCl. The precipitate was collected by filtration to afford an off white solid (2.36 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (dt, J = 1.41, 7.65 Hz, 1H), 7.76 (*app* t, J = 1.68 Hz, 1H), 7.69-7.53 (m, 3H), 7.36-7.14 (m, 2H), 6.69 (s, 1H), 5.32 (s, 2H), 1.93 (s, 3H). ES-HRMS m/z 406.0662 (M+H $C_{20}H_{14}ClF_2NO_4$ requires 406.0652).

Example 292

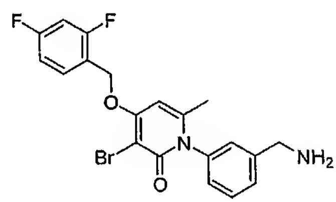


3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

The starting material (0.550 g, 1.540 mmol) and *N*-chlorosuccinimide (0.214 g, 1.602 mmol) were suspended in dichloromethane (15 mL). Dichloroacetic acid (0.01 ml, 0.154

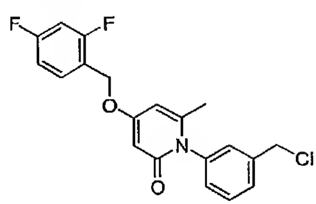
mmol) was added and the reaction mixture heated to 40 °C for 9 hours. The reaction was cooled to room temperature and a precipitate formed. The precipitate was collected by filtration and washed with dichloromethane (3 x 10 mL) to afford a white solid (0.286 g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (*app* q, J = 7.35 Hz, 1H), 7.30-7.24 (m, 2H), 7.00 (br s, 1H), 6.85 (*app* dt, J = 2.37, 6.24 Hz, 1H), 6.82-6.67 (m, 2H), 6.01 (s, 1H), 5.07 (s, 2H), 4.48 (d, J = 5.24 Hz, 2H), 1.81 (*app* d, J = 0.40 Hz, 3H). ES-HRMS m/z 392.0885 (M+H $C_{20}H_{16}ClF_2NO_3$ requires 392.0860).

Example 293



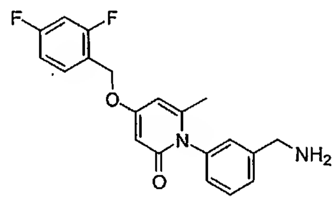
1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.



2,4,6-Trichloro-[1,3,5]-triazine (3.09 g, 16.78 mmol) was dissolved in *N,N*-dimethylformamide (45 mL). The reaction mixture was stirred at room temperature for 1 hour and then dichloromethane (90 mL) was added. The alcohol (5.72 g, 15.99 mmol) was then added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (200 mL) and the organic phase was washed with H_2O (200 mL), saturated Na_2CO_3 (200 mL), 1*N* HCl (200 mL), and brine (200 mL). The organic phase was dried over $MgSO_4$ and evaporated to give an orange solid (5.95 g, 99%).

Step 2: Preparation of 1-[3-(aminomethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6- methylpyridin-2(1H)-one.

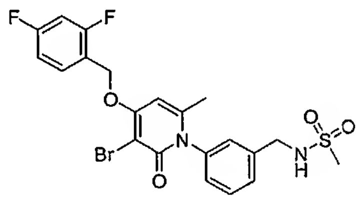


1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one from step 1 (1.00 g, 2.66 mmol) was suspended in methanol (5 mL). The suspension was then brought to -78 °C and NH_3 was bubbled through the reaction mixture for 10 minutes. The reaction was then slowly allowed to warm to room temperature and stirred at room temperature for 4 days. The reaction was concentrated and the residue taken up in CH_2Cl_2 and filtered to remove excess salt. The filtrate was concentrated to afford a tan solid (0.94 g, 99%).

Step 3: Preparation of title compound . 1-[3-(aminomethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-

methylpyridin-2(1H)-one from step 3 (3.89 g, 10.93 mmol) suspended in acetonitrile (42 mL) was cooled in an ice-bath. *N*-bromosuccinimide (2.04 g, 11.47 mmol) was added and the ice-bath was removed. The reaction mixture was stirred for 1.5 hours at room temperature. The reaction was diluted with acetonitrile (100 mL) and the precipitate that formed was collected by filtration and washed with acetonitrile (3 x 30 mL) to afford an off-white solid (2.74 g, 58%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.67-7.59 (m, 3H), 7.34-7.31 (m, 2H), 7.04 (*app* t, *J* = 8.72 Hz, 2H), 7.05-6.88 (m, 2H), 6.13 (s, 1H), 5.30 (s, 2H), 3.95 (s, 1H), 2.01 (s, 3H). ES-HRMS *m/z* 435.0538 (M+H $C_{20}H_{17}BrF_2N_2O_2$ requires 435.0514).

Example 294

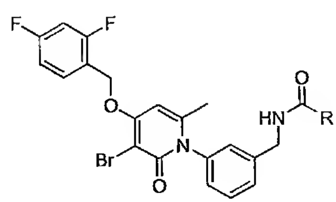


N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}methanesulfonamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 293 (0.200 g, 0.459 mmol) and *N,N*-dimethylformamide (4 mL). A stock solution of 4-methylmorpholine in *N,N*-dimethylformamide (1.8 mL, 1.0 M) was added to the reaction vessel and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes. A stock solution of

methanesulfonyl chloride in *N,N*-dimethylformamide (4.50 mL, 0.15 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 2 hours. At this time the reaction was diluted with dichloromethane (4 mL) and treated with approximately 2.1 g of polyamine resin (2.63 mmol/g) and approximately 0.8 g of methylisocyanate functionalized polystyrene (1.7 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 5 mL). The filtrate was evaporated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give a yellow solid (0.190 g, 81%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (*app* q, *J* = 7.00 Hz, 1H), 7.56-7.50 (m, 2H), 7.25 (m, 1H), 7.16 (dt, *J* = 1.94, 7.25 Hz, 1H), 7.04 (*app* t, *J* = 8.59 Hz, 2H), 6.58 (s, 1H), 5.34 (s, 2H), 4.30 (s, 2H), 2.87 (s, 3H), 2.03 (s, 3H). ES-HRMS *m/z* 513.0313 (M+H $C_{21}H_{19}BrF_2N_2O_4S$ requires 513.0290).

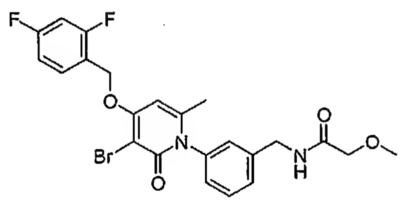
Preparation of Example 295-296



By following the method of Example 294 and replacing methanesulfonyl chloride with the appropriate acid chloride, the compounds of Examples 295-296 are prepared.

Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 295	CH_3	78.0	$C_{22}H_{19}BrF_2N_2O_3$	477.0620	477.0640
Ex. 296	OCH_3	84.0	$C_{22}H_{19}BrF_2N_2O_4$	493.0569	493.0591

Example 297

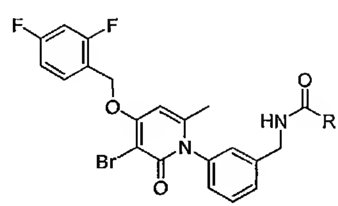


N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-2-methoxyacetamide

To a reaction vessel (borosilicate culture tube) was added approximately 2.87 g of polymer bound carbodiimide resin (0.96 mmol/g) followed by a stock solution of methoxyacetic acid (8.0 mL, 0.10 M) in *N,N*-dimethylacetamide. A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylacetamide (3.0 mL, 0.10 M) and *N*-methylmorpholine (6.0 mL, 0.10 M) in 1,2-dichloroethane were added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 4 hours. A stock solution of EXAMPLE 293 in

N,N-dimethylacetamide (5.0 mL, 0.10 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with 1,2-dichloroethane (10 mL) and treated with approximately 1.70 g of polyamine resin (2.63 mmol/g) and approximately 0.84 g of methylisocyanate functionalized polystyrene (1.50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with *N,N*-dimethylacetamide (2 x 5 mL). The filtrate was evaporated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off white solid (0.081 g, 28%). ^{1}H NMR (400 MHz, DMF-d_6) δ 7.59 (q, J = 7.65 Hz, 1H), 7.46 (*app* t, J = 7.55 Hz, 1H), 7.40-7.37 (m, 1H), 7.11-7.07 (m, 2H), 7.00 (t, J = 8.56 Hz, 2H), 6.54 (s, 1H), 5.30 (s, 2H), 4.43 (s, 2H), 3.88 (s, 2H), 3.35 (*app* d, J = 0.80 Hz, 2H), 1.97 (s, 3H). ES-HRMS *m/z* 507.0699 (M+H $C_{23}H_{21}BrF_2N_2O_4$ requires 507.0726).

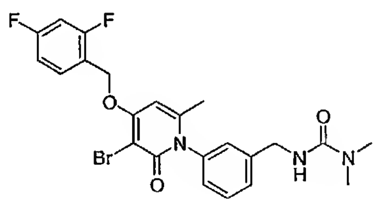
Preparation of Examples 298-300



By following the method of and replacing methoxyacetic acid with the appropriate acid, the compounds of Examples 298-300 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane or 1 M K_2CO_3 in methanol to afford the compounds as hydrochloride salts.

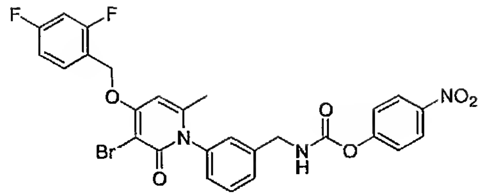
Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS *m/z*
Ex. 298	CH_2OCOCH_3	35.5	$C_{24}H_{21}BrF_2N_2O_5$	535.0675	535.0686
Ex. 299	CH_2NH_2	32.6	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0744
Ex. 300	CH_2OH	33.4	$C_{22}H_{19}BrF_2N_2O_4$	493.0569	493.0578

Example 301



N'-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-N,N-dimethylurea

Step 1: Preparation of 4-nitrophenyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzylcarbamate.

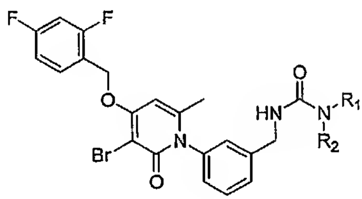


1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1.08 g, 2.48 mmol) was suspended in dichloromethane (7.5 mL). Pyridine was added (0.222 mL, 2.74 mmol). After stirring for 10 minutes at room temperature, a stock solution of 4-nitrophenyl chloroformate (5.0 mL, 0.50 M) in dichloromethane was added dropwise. After stirring for 4.5 hours at room temperature, a stock solution of 4-nitrophenyl chloroformate (2.5 mL, 0.50 M) in dichloromethane was again added dropwise and stirring continued at room temperature overnight. The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded a yellow solid (0.85 g, 57%).

Step 2: Preparation of title compound . To a reaction vessel (borosilicate culture tube) was added 4-nitrophenyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzylcarbamate (from step 1) (0.150 g, 0.250 mmol) and dichloromethane (2.5 mL). The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. A stock solution of *N,N*-dimethylamine in tetrahydorfuran (0.15 mL, 2.0 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off white solid (0.065

g, 51%). ^{1}H NMR (400 MHz, DMF-d_6) δ 7.58 (*app* q, *J* = 7.79 Hz, 1H), 7.42 (*app* t, *J* = 7.65 Hz, 1H), 7.37 (*app* d, *J* = 7.79 Hz, 1H), 7.08 (s, 1H), 7.03 (*app* dt, *J* = 1.58, 5.37 Hz, 1H), 6.96 (*app* dt, *J* = 2.55, 8.39 Hz, 1H), 6.88-6.83 (m, 1H), 6.06 (s, 1H), 5.24 (s, 2H), 4.95 (*app* t, *J* = 5.57 Hz, 1H), 4.42 (*app* dddd, *J* = 5.10, 5.71, 10.20, 15.17 Hz, 2H), 2.90 (s, 6H), 1.96 (s, 3H). ES-HRMS *m/z* 506.0848 (M+H $C_{23}H_{22}BrF_2N_3O_3$ requires 506.0885).

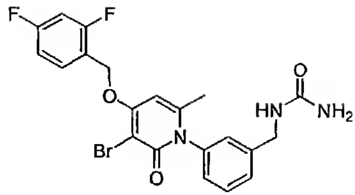
Preparation of Examples 302-303



By following the method of Example 301 and substituting *N,N*-dimethylamine with the appropriate amine, the compounds of Examples 302-303 are prepared.

Compound No.	R_1	R_2	% Yield	MF	M+H Requires	ES-HRMS *m/z*
Ex. 302	H	CH_3	52.3	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0737
Ex. 303	CH_2CH_2O-	CH_2CH_2O-	50.7	$C_{25}H_{24}BrF_2N_3O_4$	548.0991	548.0962

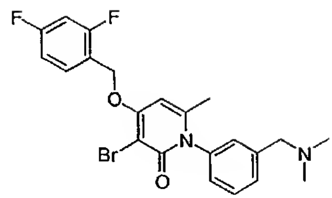
Example 304



N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}urea

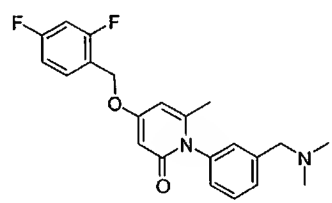
To a reaction vessel (borosilicate culture tube) was added EXAMPLE 293 (0.200 g, 0.459 mmol) and tetrahydrofuran (4.0 mL). A stock solution of 4-methylmorpholine in tetrahydrofuran (1.8 mL, 1.0 M) was added to the reaction vessel and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes. A stock solution of trimethylsilyl isocyanate in tetrahydrofuran (4.0 mL, 0.2 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for two hours. At this time the reaction was diluted with tetrahydrofuran (4.0 mL) and the resulting precipitate collected by filtration. The solid was then washed with tetrahydrofuran (3 x 5 mL) to afford a white solid (0.214 g, 97%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (*app* q, *J* = 7.83 Hz, 1H), 7.55 (*app* t, *J* = 8.06 Hz, 1H), 7.46 (d, *J* = 7.52 Hz, 1H), 7.25-7.14 (m, 4H), 6.65 (s, 1H), 5.65 (*app* t, *J* = 0.80 Hz, 1H), 5.40 (s, 2H), 4.38 (s, 2H), 2.05 (s, 3H). ES-HRMS *m/z* 478.0594 (M+H $C_{21}H_{18}BrF_2N_3O_3$ requires 478.0572).

Example 305



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one

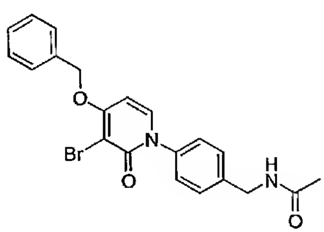
Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one.



1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (from step 1 of the synthesis of EXAMPLE 293) (0.500 g, 1.330 mmol) was suspended in a stock solution of *N,N*-dimethylamine in methanol (2.0 mL, 2.0 M) and stirred overnight at room temperature. Reaction was concentrated and the residue partitioned between H_2O (25 mL) and ethyl acetate (25 mL). The aqueous layer was further extracted with ethyl acetate (2 x 30 mL), and the combined organics were washed with brine (30 mL), dried over $MgSO_4$, and concentrated to afford an off-white solid (0.508 g, 99%).

Step 2: Preparation of the title compound . 4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one from step 1 (0.200 g, 0.521 mmol) was suspended in acetonitrile (2.5 mL) and cooled in an ice-bath. *N*-bromosuccinimide (0.097 g, 0.547 mmol) was added and the ice-bath was removed. The reaction mixture was stirred for 1.5 hours at room temperature. The reaction was diluted with acetonitrile (100 mL). The precipitate that formed was collected by filtration and washed with acetonitrile (3 x 15 mL) to afford a yellow solid (0.160 g, 66%). Chromatography (C-18, acetonitrile/H_2O with 0.1% trifluoroacetic acid, followed by chromatography silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off-white solid (0.024 g, 10%). ^1H NMR (400 MHz, CD_3OD) δ 7.68 (*app* q, *J* = 7.85 Hz, 1H), 7.58 (*app* t, *J* = 7.65 Hz, 1H), 7.50 (*app* d, *J* = 7.85 Hz, 1H), 7.25-7.05 (m, 4H), 6.63 (s, 1H), 5.39 (s, 2H), 3.61 (*app* q, *J* = 12.08 Hz, 2H), 2.32 (s, 6H), 2.08 (s, 3H). ES-HRMS *m/z* 463.0782 (M+H $C_{22}H_{21}BrF_2N_2O_2$ requires 463.0827).

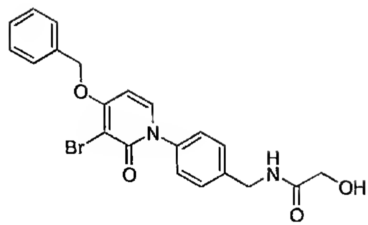
Example 306



N-{4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzyl}acetamide

1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one hydrochloride (0.150 g, 0.389 mmol) was dissolved in *N,N*-dimethylformamide (3.5 mL). A stock solution of 4-methylmorpholine in *N,N*-dimethylformamide (1.5 mL, 1.0 M) was added and the reaction stirred at room temperature for 10 minutes. A stock solution of acetyl chloride in *N,N*-dimethylformamide (3.0 mL, 0.2 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at 200 RPM for 2 hours at room temperature. At this time the reaction was diluted with dichloromethane (4 mL) and treated with approximately 1.8 g of polyamine resin (2.63 mmol/g) and approximately 0.8 g of methylisocyanate functionalized polystyrene (1.7 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were further rinsed with dichloromethane (3 x 5 mL) and combined with the partially concentrated filtrate. The resulting filtrate was concentrated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0.083 g, 50%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, *J* = 7.79 Hz, 1H), 7.48-7.29 (m, 9H), 6.55 (d, *J* = 7.79 Hz, 1H), 5.35 (s, 2H), 4.39 (s, 2H), 1.98 (s, 3H). ES-HRMS *m/z* 427.0625 (M+H $C_{21}H_{19}BrN_2O_3$ requires 427.0652).

Example 307

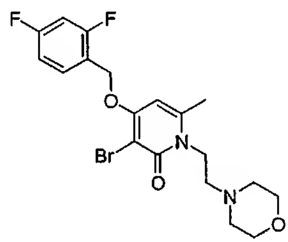


N-{4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzyl}-2-hydroxyacetamide

To a reaction vessel (borosilicate culture tube) was added approximately 1.95 g of polymer bound carbodiimide resin (0.96 mmol/g) followed by a stock solution of glycolic acid (5.8 mL, 0.10 M) in *N,N*-dimethylacetamide. A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylacetamide (0.4 mL, 0.10 M) and *N*-methylmorpholine in 1,2-dichloroethane (3.9 mL, 0.10 M) were added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 2 hours. A stock solution of 1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one hydrochloride in *N,N*-dimethylacetamide (0.05 M, 7.8 mL) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with 1,2-dichloroethane (8 mL) and treated with approximately 1.17 g of polyamine resin (2.63 mmol/g) and approximately 0.58 g of methylisocyanate functionalized polystyrene (1.50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After

partial evaporation the insoluble byproducts were rinsed with *N,N*-dimethylacetamide (2 x 5 mL) and combined with the partially concentrated filtrate. The filtrate was concentrated by blowing N_2 over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off white solid (0.081 g, 21%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.30 (m, 10H), 6.51 (d, *J* = 7.85 Hz, 1H), 5.37 (s, 2H), 4.52 (s, 2H), 4.08 (s, 2H). ES-HRMS *m/z* 443.0605 (M+H $C_{21}H_{19}BrN_2O_4$ requires 443.0601).

Example 308

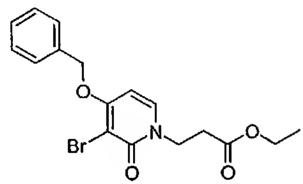


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-morpholin-4-ylethyl)pyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.100 g, 0.303 mmol), cesium carbonate (0.296 g, 0.909 mmol), and 4-(2-chloroethyl)morpholine (0.059 g, 0.394 mmol) were suspended in acetonitrile (4 mL). The reaction was stirred at 60 °C overnight. H_2O (25 mL) was added and the resulting precipitate was collected by filtration. The solid was subjected to chromatography (silica gel, ethyl acetate with 10% methanol) afforded an off-white solid (0.040 g, 30%). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.55 (*app* q, *J* = 7.92 Hz, 1H), 6.93 (*app* t, *J* = 8.39 Hz, 1H), 6.84 (*app* t, *J* = 9.40 Hz, 1H), 5.95 (s, 1H), 5.18 (s, 2H), 4.16 (*app* t, *J* = 6.78 Hz, 2H), 3.68 (s, 4H), 2.65 (*app* t, *J* = 6.38 Hz, 2H), 2.54 (s, 4H), 2.43 (s, 3H). ES-HRMS *m/z* 443.0743 (M+H $C_{19}H_{21}BrF_2N_2O_3$ requires 443.0776).

Example 309

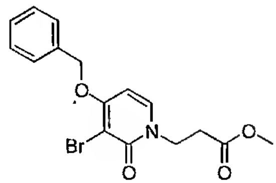


ethyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]propanoate

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.50 g, 1.78 mmol) and cesium fluoride (0.0027 g, 0.178 mmol) were suspended in tetrahydrofuran (10 mL) followed by dropwise addition of tetraethylortho silicate (0.37 g, 1.78 mmol) at room temperature. After stirring for 10 minutes at room temperature, ethyl acrylate (0.23 g, 2.32 mmol) was added dropwise and the reaction stirred at room temperature overnight. The reaction mixture was filtered through a pad of Celite®. The filtrate was concentrated and the resulting residue subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a white solid (0.62 g, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.79 Hz, 1H), 7.41-7.29 (m, 5H), 6.03 (d, *J* = 7.65 Hz, 1H), 5.20 (s, 2H), 4.17 (t, *J* = 5.98 Hz, 2H), 4.07 (q, *J* = 7.16 Hz, 2H), 2.83 (t,

J = 5.98 Hz, 2H), 1.19 (t, J = 7.18 Hz, 3H). ES-HRMS m/z 380.0523 (M+H $C_{17}H_{18}BrNO_4$ requires 380.0492).

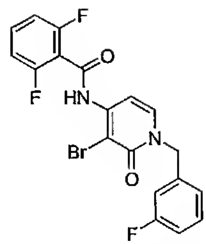
Example 310



methyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]propanoate

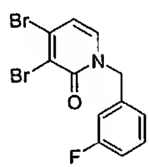
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (5.00 g, 17.85 mmol) and cesium fluoride (0.27 g, 1.78 mmol) were suspended in tetrahydrofuran (50 mL) followed by dropwise addition of tetramethylortho silicate (2.70 g, 17.85 mmol) at room temperature. After stirring for 10 minutes at room temperature, methyl acrylate (2.00 g, 23.20 mmol) was added dropwise and the reaction stirred at room temperature for 48 hours. The reaction mixture was filtered through a pad of Celite®. The filtrate was concentrated and the resulting residue subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a white solid (6.10 g, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.65 Hz, 1H), 7.41-7.29 (m, 5H), 6.04 (d, J = 7.65 Hz, 1H), 5.20 (s, 2H), 4.17 (t, J = 5.91 Hz, 2H), 3.63 (s, 3H), 2.85 (t, J = 5.91 Hz, 2H). ES-HRMS m/z 366.0350 (M+H $C_{16}H_{16}BrNO_4$ requires 366.0335).

Example 311



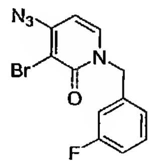
N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,6-difluorobenzamide

Step 1: Preparation of 3,4-dibromo-1-(3-fluorobenzyl)pyridin-2(1H)-one.



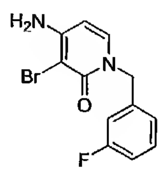
3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (2.00 g, 4.65 mmol), KBr (5.53 g, 46.49 mmol), and 18-Crown-6 (0.10 g, 0.38 mmol) were dissolved in *N,N*-dimethylacetamide (26 mL). The reaction mixture was then heated at reflux for 16 hours. The reaction was concentrated and the resulting residue was partition between water (50 mL) and ethyl acetate (3 X 50 mL). The combined organics were washed with H_2O (2 X 30 mL), brine (50 mL), dried over $MgSO_4$, concentrated, and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexane) to afford a brown solid (0.850 g, 51%).

Step 2: Preparation of 4-azido-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one.



Sodium azide (1.08 g, 16.62 mmol) was suspended in *N,N*-dimethylformamide (10 mL) and a stock solution of 3,4-dibromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 1) in *N,N*-dimethylformamide (33.0 mL, 0.33 M) was added and the resulting mixture was heated to 60 °C for 4 hours. Ice water (30 mL) was added and the aqueous layer was extracted with ethyl acetate (4 X 50 mL). The combined organics were washed with H_2O (3 X 50 mL), brine (2 X 25 mL), dried over $MgSO_4$, concentrated, and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexane) to afford an off-white solid (3.50 g, 98%).

Step 3: Preparation of 4-amino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one hydrochloride

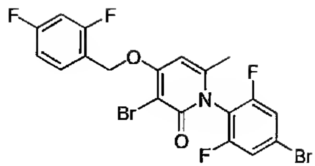


4-azido-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 2) (4.00 g, 12.38 mmol) was suspended in ethyl acetate (300 mL) and Fe (2.07 g, 37.14 mmol) was added. A stock solution

of NH_4Cl in H_2O (300 mL, 0.2 M) was added and the reaction mixture was stirred at room temperature for 36 hours. The reaction was filtered through a pad of Celite® and concentrated. The resulting solid was dissolved in ethyl acetate (150 mL) and washed with water (3 X 50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated. ^1H NMR (400 MHz, CD_3OD) δ 7.38-7.29 (m, 2H), 7.05 (d, J = 7.79 Hz, 1H), 6.99 (d, J = 8.99 Hz, 2H), 6.03 (d, J = 7.39 Hz 1H), 5.09 (s, 2H). ES-HRMS m/z 297.0023 (M+H $C_{20}H_{17}BrF_2N_2O_2$ requires 297.0033).

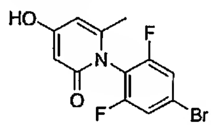
Step 4: Preparation of the title compound . 4-amino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 3) (0.30 g, 1.01 mmol) and 4-dimethylaminopyridine (0.002 g, 0.01 mmol) were suspended in acetonitrile (5 mL) followed by dropwise addition of triethylamine (0.2 mL, 1.41 mmol). This reaction mixture was stirred for 10 minutes at room temperature before being cooled to 0 °C. 2,6-difluorobenzoyl chloride (0.37 g, 2.12 mmol) was added dropwise and the reaction was heated at reflux overnight. The reaction was cooled to room temperature and 1*N* NaOH (10 mL) was added. The reaction was then stirred for 45 minutes at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the organic layer washed with 1*N* NaOH (2 X 25 mL), H_2O (until pH neutral), brine (50 mL), dried over $MgSO_4$, concentrated, and subjected to chromatography (on C-18, acetonitrile/ H_2O with 0.1% trifluoracetic acid) to afford a white solid (0.19 g, 43%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.67 (d, J = 7.65 Hz, 1H), 7.49 (*app* tt, J = 6.31, 8.60 Hz, 1H), 7.33-28 (m, 2H), 7.10-6.97 (m, 5H), 5.17 (s, 2H). ES-HRMS m/z 437.0083 (M+H $C_{19}H_{12}BrF_3N_2O_2$ requires 437.0107).

Ex. 312



3-bromo-1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

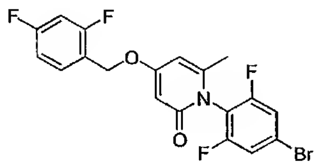
Step 1: Preparation of 1-(4-bromo-2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one .



4-Hydroxy-6-methyl-2-pyrone (30.0 g, 238 mmol) and 4-bromo-2,6-difluoroaniline (49.5 g, 238 mmol) were suspended in 50 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked, round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 80°C. The flask was placed in an ice bath and about 25 ml of toluene was added and stirred. After about 10 minutes, a precipitate formed. The precipitate was filtered and washed 3 times with toluene, 3 times with hot water to remove excess pyrone, and dried *in vacuo* to give a tan solid (22.1 g, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (br s, 1H), 7.71 (d, J = 6.98 Hz, 2H), 5.97 (t, J = 0.88 Hz, 1H), 5.55 (d, J = 2.28 Hz, 1H), 1.91 (s, 3H). LC/MS, t_r = 1.96 minutes (5 to 95% acetonitrile/water over 5

minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 316 (M+H). ES-HRMS *m/z* 315.9779 (M+H calcd for $C_{12}H_8BrF_2NO_2$ requires 315.9779).

Step 2: Preparation of 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one .

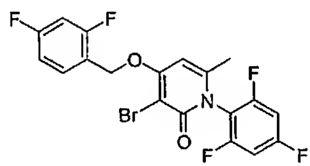


1-(4-bromo-2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (from Step 1) (5.0 g, 15.8 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (2.23 ml, 17.4 mmol) and K_2CO_3 (3.27 g, 23.7 mmol) in 50 ml of dimethylformamide. After stirring overnight, the reaction was poured quickly into 900 ml of cold water. The resulting precipitate was filtered and washed with water and hexane. The product was purified using a Biotage silica chromatography system using 20% ethyl acetate/hexanes to give a beige solid (4.32 g, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (app q, *J* = 6.31 Hz, 1H), 7.25 (dd, *J* = 8.33, 1.74 Hz, 2H), 6.91 (dt, *J* = 9.2, 0.8 Hz, 1H), 6.86 (dt, *J* = 9.2, 0.8 Hz, 1H), 5.95 (d, *J* = 2.56 Hz, 1H), 5.92 (dd, *J* = 2.56, 0.94 Hz, 1H), 5.01 (s, 2H), 1.98 (s, 3H). LC/MS, t_r = 3.04 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 442 (M+H). ES-HRMS *m/z* 442.0057 (M+H calcd for $C_{19}H_{12}BrF_4NO_2$ requires 442.0060).

Step 3: Preparation of the title compound . 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-

2(1H)-one (from Step 2) (500 mg, 1.13 mmol) was stirred at room temperature with *N*-bromosuccinimide (221 mg, 1.24 mmol) in 5 ml of CH_2Cl_2 for 1.5 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (478 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (*app* q, *J* = 6.64 Hz, 1H), 7.31 (d, *J* = 6.85 Hz, 2H), 7.01 (*app* t, *J* = 8.36 Hz, 1H), 6.96 (dt, *J* = 9.46, 2.21 Hz, 1H), 6.19 (s, 1H), 5.30 (s, 2H), 2.10 (s, 3H); LC/MS, t_r = 3.17 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 520 (M+H). ES-HRMS *m/z* 521.9134 (M+H calcd for $C_{19}H_{11}Br_2F_4NO_2$ requires 521.9146).

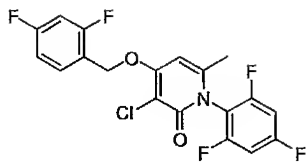
Ex. 313



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

The title compound was produced essentially as in Example 313, using 2,4,6-trifluoroaniline instead of 4-bromo-2,6-difluoroaniline. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (*app* q, *J* = 7.79 Hz, 1H), 7.01 (*app* dt, *J* = 8.26, 2.01 Hz, 1H), 6.95 - 6.85 (m, 3H), 6.19 (s, 1H), 5.30 (s, 2H), 2.11 (s, 3H); LC/MS, t_r = 2.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 460 (M+H). ES-HRMS *m/z* 459.9954 (M+H calcd for $C_{19}H_{11}BrF_5NO_2$ requires 459.9966).

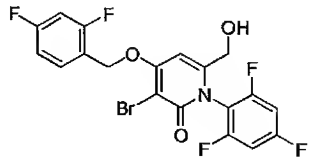
Ex. 314



3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

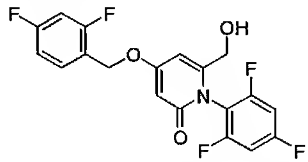
4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (350 mg, 0.92 mmol) was refluxed with *N*-chlorosuccinimide (147 mg, 1.1 mmol) and dichloroacetic acid (0.038 ml, 0.46 mmol) in 5 ml of CH_2Cl_2 overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (217 mg, 57%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (*app* q, *J* = 7.75 Hz, 1H), 7.00 (*app* dt, *J* = 8.23, 2.05 Hz, 1H), 6.93 - 6.86 (m, 3H), 6.22 (s, 1H), 5.30 (s, 2H), 2.12 (s, 3H); LC/MS, t_r = 2.78 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 416 (M+H). ES-HRMS *m/z* 416.0472 (M+H calcd for $C_{19}H_{11}ClF_5NO_2$ requires 416.0471).

Ex. 315



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one .

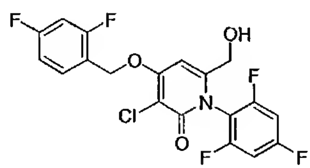


4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (9.0 g, 23.6 mmol) was heated to 135°C overnight with SeO_2 (13.1 g, 118 mmol) in 75 ml of 1,4-dioxane in a 350 ml sealed glass pressure vessel. The reaction mixture was cooled and placed on a plug of silica gel and washed with 5% methanol in CH_2Cl_2. The filtrate was evaporated and the resulting solid was washed with diethyl ether and dissolved in hot ethyl acetate. The insoluble Se salts were filtered off and the organic layer was evaporated. 7.01g (17.6 mmol) of a 3:1 ratio of aldehyde to desired alcohol was isolated. The mixture was stirred with $NaBH_4$ (802 mg, 21.2 mmol) in 30 ml of methanol at room temperature for 1 hour. The reaction was evaporated and CH_2Cl_2 and acetonitrile were used to dissolve the bulk of the solid. The remaining insoluble solid was filtered off. The organic layer was washed 3 times with NH_4Cl, dried over $MgSO_4$ and evaporated. The resulting solid was washed 3 times with diethyl ether and dried *in vacuo* to yield a light orange solid (4.35 g, 46%). ^1H NMR (300 MHz, DMSO-d_6) δ 7.68 (*app* q, J = 7.92 Hz, 1H), 7.47 (*app* t, J = 8.57 Hz, 2H), 7.35 (dt, J = 9.87, 2.42 Hz, 1H), 7.18 (dt, J = 8.31, 1.71 Hz, 1H), 6.21 (d, J = 2.42 Hz, 1H), 6.07 (d, J = 2.62 Hz, 1H), 5.67 (br s, 1H), 5.18 (s, 2H), 3.98

(s, 2H); LC/MS, t_r = 2.31 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 398 (M+H).

Step 2: Preparation of the title compound. 4-[(2,4-Difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (from step 1) (2.1 g, 5.28 mmol) was stirred at room temperature with *N*-bromosuccinimide (1.13 g, 6.34 mmol) in 5 ml CH_2Cl_2 for 2 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (1.35 g, 54%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (*app* q, *J* = 6.65 Hz, 1H), 7.20 (*app* t, *J* = 8.36 Hz, 2H), 7.09 (*app* t, *J* = 8.46 Hz, 2H), 6.88 (s, 1H), 5.46 (s, 2H), 4.21 (s, 2H); LC/MS, t_r = 2.48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 476 (M+H). ES-HRMS *m/z* 475.9907 (M+H calcd for $C_{19}H_{11}BrF_5NO_3$ requires 475.9915).

Ex. 316

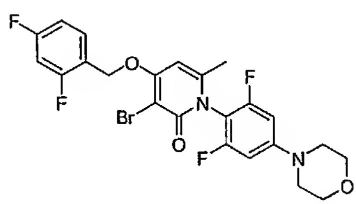


3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

4-[(2,4-Difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (2.1 g, 5.28 mmol) was

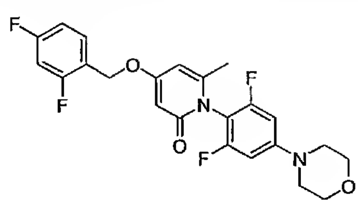
refluxed with *N*-chlorosuccinimide (846 mg, 6.34 mmol) and dichloroacetic acid (0.87 ml, 10.56 mmol) in 5 ml CH_2Cl_2 overnight. The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with diethyl ether to obtain a solid. The solid was washed 4 times with acetonitrile. Chromatography was done using a Biotage silica gel system with 60% ethyl acetate/hexanes. The recovery was poor from the column to give a white solid (109 mg, 5%). ^1H NMR (300 MHz, CD_3OD) δ 7.67 (*app* q, *J* = 7.85 Hz, 1H), 7.24 - 7.06 (m, 4H), 6.90 (s, 1H), 5.45 (s, 2H), 4.22 (s, 2H); LC/MS, t_r = 2.71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 432 (M+H). ES-HRMS *m/z* 432.0413 (M+H calcd for $C_{19}H_{11}ClF_5NO_3$ requires 432.0420).

Ex. 317



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one

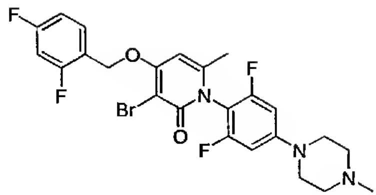
Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one .



4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (870 mg, 2.28 mmol) was heated to 100°C with K_2CO_3 (630 mg, 4.56 mmol) in 5 ml of morpholine for 36 hours. The reaction was added to 200 ml of cold water and the resulting solid was washed with water and 50:50 diethyl ether/hexanes and dried *in vacuo* to give a beige solid (738 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (*app* q, *J* = 7.70 Hz, 1H), 6.93 - 6.85 (m, 2H), 6.49 (d, *J* = 10.47 Hz, 2H), 5.96 (d, *J* = 2.41 Hz, 1H), 5.89 (d, *J* = 1.75 Hz, 1H), 5.00 (s, 2H), 3.83 (t, *J* = 4.83 Hz, 4H), 3.19 (t, *J* = 4.84 Hz, 4H), 1.99 (s, 3H); LC/MS, t_r = 3.09 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 449 (M+H). ES-HR/MS *m/z* 449.1485 (M+H calcd for $C_{23}H_{20}F_4N_2O_3$ requires 449.1483).

Step 2: Preparation of the title compound . 4-[(2,4-Difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one (from step 1) (500 mg, 1.12 mmol) was stirred at room temperature with *N*-bromosuccinimide (236 mg, 1.33 mmol) in 5 ml of CH_2Cl_2 for 2 hours. The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with diethyl ether to obtain a solid. The solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (171 mg, 29%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (*app* q, *J* = 7.74 Hz, 1H), 6.96 (*app* t, *J* = 8.39 Hz, 1H), 6.86 (dt, *J* = 9.46, 2.28 Hz, 1H), 6.50 (d, *J* = 10.74 Hz, 2H), 6.09 (s, 1H), 5.24 (s, 2H), 3.84 (t, *J* = 4.84 Hz, 4H), 3.20 (t, *J* = 4.83 Hz, 4H), 2.07 (s, 3H); LC/MS, t_r = 3.18 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 527 (M+H). ES-HRMS *m/z* 527.0570 (M+H calcd for $C_{23}H_{19}BrF_4N_2O_3$ requires 527.0588).

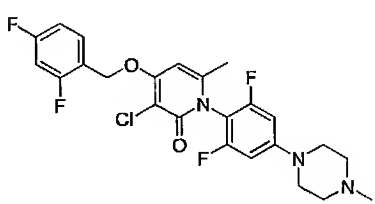
Ex. 318



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared essentially as in Example 317, using 1-methylpiperazine instead of morpholine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (*app* q, *J* = 7.79 Hz, 1H), 6.96 (dt, *J* = 8.19, 1.88 Hz, 1H), 6.86 (*app* dt, *J* = 9.44, 2.48 Hz, 1H), 6.52 (d, *J* = 10.61 Hz, 2H), 6.14 (s, 1H), 5.24 (s, 2H), 3.72 (br s, 4H), 3.51 (d, *J* = 11.27 Hz, 2H), 3.07 (br s, 2H), 2.85 (d, *J* = 4.29 Hz, 3H), 2.06 (s, 3H); LC/MS, t_r = 2.50 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 540 (M+H). ES-HRMS *m/z* 540.0930 (M+H calcd for $C_{24}H_{22}BrF_4N_3O_2$ requires 540.0904).

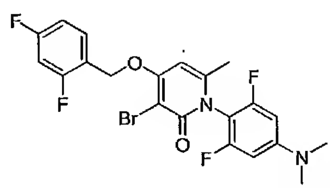
Ex. 320



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

4-[(2,4-Difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one (1.3 g, 2.82 mmol) was stirred at reflux with *N*-chlorosuccinimide (451 mg, 3.38 mmol) and dichloroacetic acid (0.17 ml, 1.41 mmol) in 6 ml CH_2Cl_2 overnight. LC-MS showed 33% completion. More *N*-chlorosuccinimide (271 mg, 2.23 mmol) was added and refluxed overnight. The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with ethyl acetate to obtain a solid. The solid was washed 4 times with ethyl acetate and with diethyl ether and dried in vacuo to obtain a white solid (606 mg, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (br q, J = 7.74 Hz, 1H), 7.33 (br t, J = 9.00 Hz, 1H), 7.16 (br t, J = 7.65 Hz, 1H), 6.96 (d, J = 11.81 Hz, 2H), 6.79 (s, 1H), 5.33 (s, 2H), 3.61 (br m, 4H), 3.25 (br m, 4H), 3.21 (br s, 3H), 2.04 (s, 3H); LC/MS, t_r = 2.45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 496 (M+H). ES-HRMS m/z 496.1400 (M+H calcd for $C_{24}H_{22}ClF_4N_3O_2$ requires 496.1409).

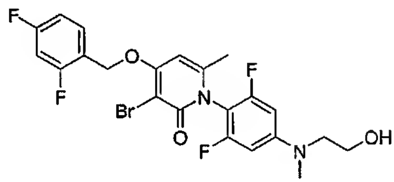
Example 321



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared essentially as described in Example 317, using dimethylamine instead of morpholine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (q, J = 7.74 Hz, 1H), 6.95 (dt, J = 8.32, 1.61 Hz, 1H), 6.85 (*app* dt, J = 9.54, 2.41 Hz, 1H), 6.27 (d, J = 11.01 Hz, 2H), 6.08 (s, 1H), 5.23 (s, 2H), 2.98 (s, 3H), 2.07 (s, 3H); LC/MS, t_r = 3.35 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 485 (M+H). ES-HRMS m/z 485.0447 (M+H calcd for $C_{21}H_{17}BrF_4N_2O_2$ requires 485.0482).

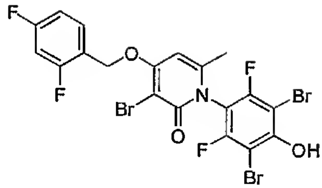
Example 322



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1H)-one

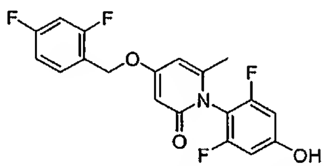
The title compound was prepared essentially as in Example 317, using 2-(methylamino)ethanol instead of morpholine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (q, J = 7.74 Hz, 1H), 6.95 (dt, J = 8.24, 1.66 Hz, 1H), 6.85 (*app* dt, J = 9.49, 2.37 Hz, 1H), 6.35 (d, J = 11.01 Hz, 2H), 6.10 (s, 1H), 5.23 (s, 2H), 3.77 (t, J = 5.77 Hz, 2H), 3.45 (t, J = 5.78 Hz, 2H), 2.99 (s, 3H), 2.08 (s, 3H); LC/MS, t_r = 2.96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 515 (M+H). ES-HRMS m/z 515.0576 (M+H calcd for $C_{22}H_{19}BrF_4N_2O_3$ requires 515.0588).

Example 323



3-bromo-1-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one .

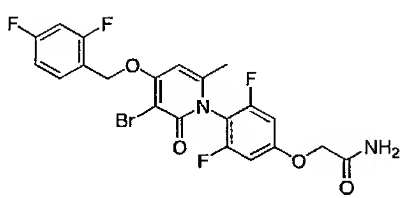


4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (step 2 above) (10.0 g, 26.2 mmol) was heated to 45°C with $KOSiMe_3$ (10.08 g, 78.6 mmol) in 50 ml of tetrahydrofuran for 4 days. The reaction was diluted with 30 ml of ethyl acetate and washed with 1N HCl and water, dried over $MgSO_4$, and evaporated to give an orange solid. The solid was stirred in hot 60% ethyl acetate/hexanes and filtered to give a white solid, which was dried *in vacuo* to obtain a white solid (3.79 g, 38%). The filtrate was found to contain a mixture of desired product and the ortho substituted regioisomer. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (*app* q, J = 7.70 Hz, 1H), 6.95 - 6.83 (m, 2H), 6.34 (d, J = 9.40 Hz, 2H), 6.05 (*app* s, 2H), 5.06 (s, 2H), 2.01 (s, 3H); LC/MS, t_r = 2.80 minutes (5 to 95% acetonitrile/water over 5 minutes at 1

ml/min, at 254 nm, at 50°C), ES-MS *m/z* 380 (M+H). ES-HRMS *m/z* 380.0926 (M+H calcd for $C_{19}H_{13}F_4NO_3$ requires 380.0904).

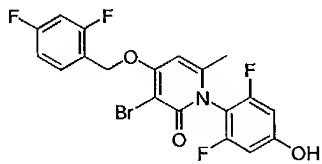
Step 2: Preparation of the title compound . 4-[(2,4-Difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one (from step 1) (3.73 g, 8.14 mmol) was stirred as a suspension at room temperature with *N*-bromosuccinimide (1.52 g, 8.55 mmol) in 30 ml CH_2Cl_2 overnight. LC-MS showed a 60% starting material. The solid was filtered off, dissolved in 30 ml of CH_2Cl_2/*N,N*-dimethylformamide and stirred with more *N*-bromosuccinimide (0.76 g, 4.28 mmol) overnight. LC-MS showed the tri-brominated product as the major product. The reaction was poured into water and extracted with n-butanol. The combined organic layers were evaporated on a rotary evaporator and the resulting solid was washed with diethyl ether and dried *in vacuo* to yield a white solid (873 mg, 17%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (*app* q, *J* = 7.80 Hz, 1H), 7.32 (dt, *J* = 4.86, 2.11 Hz, 1H), 7.16 (dt, *J* = 8.48, 1.84 Hz, 1H), 6.79 (s, 1H), 5.35 (s, 2H), 2.08 (s, 3H); LC/MS, t_r = 3.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 616 (M+H). ES-HRMS *m/z* 615.8234 (M+H calcd for $C_{19}H_{10}Br_3F_4NO_3$ requires 615.8200).

Example 324



2-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorophenoxy}acetamide

Step 1: Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one .

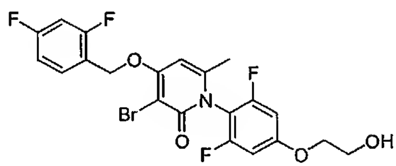


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (above) (7.5 g, 16.3 mmol) was heated to 45°C with $KOSiMe_3$ (10.08 g, 78.6 mmol) in 50 ml of tetrahydrofuran for 48 hours. The reaction was diluted with 30 ml of ethyl acetate and washed with 1N HCl and water, dried over $MgSO_4$, and evaporated to give a black oil. The oil was dissolved in ethyl acetate. A precipitate formed upon standing, which was filtered, washed with ethyl acetate and dried in vacuo to obtain a white solid (2.80 g, 37%). The filtrate showed the presence of desired product and the ortho substituted regioisomer. ^1H NMR (400 MHz, DMSO-d_6) δ 7.66 (q, J = 7.92 Hz, 1H), 7.32 (dt, J = 8.77, 2.19 Hz, 1H), 7.15 (m, 1H), 6.73 (s, 1H), 6.67 (d, J = 9.66 Hz, 2H), 5.33 (s, 2H), 2.03 (s, 3H); LC/MS, t_r = 2.92 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 458 (M+H). ES-HRMS m/z 457.9995 (M+H calcd for $C_{19}H_{12}BrF_4NO_3$ requires 458.0009).

Step 2: Preparation of the title compound . 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one (from step 1) (500 mg, 1.09 mmol) was

stirred briskly with 2-bromoacetamide (196 mg, 1.43 mmol) and K_2CO_3 (282 mg, 2.05 mmol) in 5 ml of *N,N*-dimethylformamide at room temperature for 24 hours. The reaction was poured quickly into cold water and the resulting solid was filtered, washed with water, acetonitrile, and diethyl ether, and dried *in vacuo* to give a white solid (289 mg, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (q, J = 7.92 Hz, 1H), 7.61 (br s, 1H), 7.45 (br s, 1H), 7.33 (dt, J = 10.07, 2.15 Hz, 1H), 7.16 (dt, J = 8.53, 1.88 Hz, 1H), 6.99 (d, J = 9.54 Hz, 2H), 6.76 (s, 1H), 5.34 (s, 2H), 2.03 (s, 3H); LC/MS, t_r = 2.70 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 515 (M+H). ES-HRMS m/z 515.0245 (M+H calcd for $C_{21}H_{15}BrF_4N_2O_4$ requires 515.0224).

Example 325

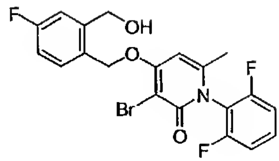


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(2-hydroxyethoxy)phenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 324. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (q, J = 7.92 Hz, 1H), 7.33 (dt, J = 10.04, 2.19 Hz, 1H), 7.17 (dt, J = 8.68, 1.84 Hz, 1H), 6.99 (d, J = 9.67 Hz, 2H), 6.75 (s, 1H), 5.34 (s, 2H), 4.92 (t, J = 4.86 Hz, 1H), 4.07 (t, J = 4.77 Hz, 2H), 3.70 (t, J = 4.83 Hz, 2H), 2.03 (s, 3H); LC/MS, t_r = 2.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 502 (M+H).

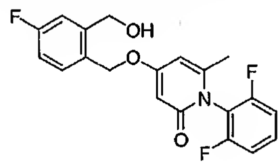
ES-HRMS m/z 502.0291 (M+H calcd for $C_{21}H_{16}BrF_4NO_4$ requires 502.0272).

Example 326



3-bromo-1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

Step 1: Preparation of 1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one .

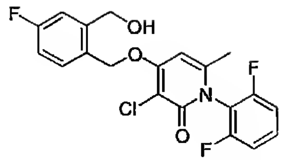


1-(2,6-Difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (step 1) (3.0 g, 12.65 mmol) was dissolved in *N,N*-dimethylformamide and cooled to 0°C. Triphenylphosphine (3.98 g, 15.18 mmol) and diethyl azodicarboxylate (2.39 ml, 15.18 mmol) were added and stirred for 10 minutes. 1,2-Bis(hydroxymethyl)-4-fluorobenzene (2.57 g, 16.44 mmol) was added and stirred at 0°C for 1 hour, then allowed to warm to room temperature and stirred overnight. LC-MS showed only 1 product, not a mixture of regioisomers, as expected. The reaction was added to water and extracted 3 times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. A Biotage silica column was done using 60% ethyl acetate/hexanes as an eluent. Desired product, with a substantial impurity was obtained. Another Biotage silica

column was ran using 30% ethyl acetate/hexanes to obtain pure product. The resulting oil was triturated with diethyl ether to obtain a white solid (720 mg, 15%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 - 7.39 (m, 2H), 7.26 (dd, *J* = 9.62, 2.51 Hz, 1H), 7.13 - 7.01 (m, 3H), 6.03 (d, *J* = 2.42 Hz, 1H), 5.96 (d, *J* = 2.41 Hz, 1H), 5.06 (s, 2H), 4.73 (s, 2H), 2.81 (br s, 1H), 2.02 (s, 3H); LC/MS, t_r = 2.37 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 376 (M+H). ES-HR/MS *m/z* 376.1181 (M+H calcd for $C_{20}H_{16}F_3NO_3$ requires 376.1155). Identity of the positional isomer was determined from hmbc, 2-D NMR experiments using H to C 2- and 3- bond coupling.

Step 2: Preparation of the title compound . 1-(2,6-Difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one (from step 1) (350 mg, 0.93 mmol) was stirred at room temperature with *N*-bromosuccinimide (199 mg, 1.12 mmol) in 1.5 ml CH_2Cl_2 for 1.5 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (197 mg, 47%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 - 7.43 (m, 2H), 7.25 (dd, *J* = 9.46, 2.62 Hz, 1H), 7.11 - 7.03 (m, 3H), 6.25 (s, 1H), 5.31 (s, 2H), 4.81 (s, 2H), 2.28 (br s, 1H), 2.10 (s, 3H); LC/MS, t_r = 2.38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 454 (M+H). ES-HRMS *m/z* 454.0247 (M+H calcd for $C_{20}H_{15}BrF_3NO_3$ requires 454.0260).

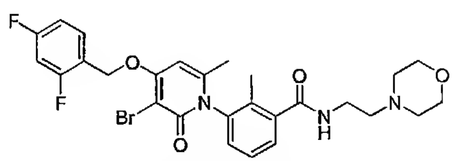
Example 327



3-chloro-1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

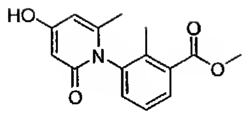
1-(2,6-Difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one (step 1 above) (275 mg, 0.73 mmol) was stirred at reflux with *N*-chlorosuccinimide (117 mg, 0.88 mmol) and dichloroacetic acid (0.03 ml, 0.36 mmol) in 1.5 ml CH_2Cl_2 overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with ethyl acetate and with diethyl ether and dried *in* vacuo to obtain a white solid (65.5 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 - 7.43 (m, 2H), 7.26 (dd, *J* = 9.38, 2.52 Hz, 1H), 7.12 - 7.04 (m, 3H), 6.27 (s, 1H), 5.32 (s, 2H), 4.82 (s, 2H), 2.29 (br s, 1H), 2.11 (s, 3H); LC/MS, t_r = 2.32 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 410 (M+H). ES-HRMS *m/z* 410.0755 (M+H calcd for $C_{20}H_{15}ClF_3NO_3$ requires 410.0765).

Example 328



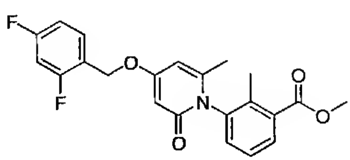
3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methyl-N-(2-morpholin-4-ylethyl)benzamide

Step 1: Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-2-methylbenzoate .



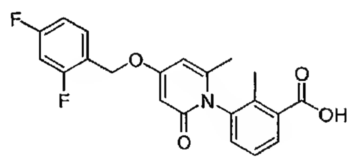
4-Hydroxy-6-methyl-2-pyrone (72.6 g, 576 mmol) and methyl-3-amino-2-methylbenzoate (100 g, 605 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 500 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 80°C. The flask was placed in an ice bath and about 300 ml of toluene was added and stirred. After about 30 minutes, a precipitate formed. The precipitate was filtered and washed 3 times with toluene, 3 times with hot water to remove excess pyrone, and dried *in vacuo* to give a tan solid (44.6 g, 28% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (br s, 1H), 7.80 (dd, *J* = 7.72, 1.28 Hz, 1H), 7.33 (dd, *J* = 7.78, 1.34 Hz, 1H), 5.91 (dd, *J* = 2.41, 0.69 Hz, 1H), 5.55 (d, *J* = 2.42 Hz, 1H), 3.82 (s, 3H), 2.06 (s, 3H), 1.73 (s, 3H); LC/MS, t_r = 1.85 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 274 (M+H). ES-HRMS *m/z* 274.1078 (M+H calcd for $C_{15}H_{15}NO_4$ requires 274.1074).

Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoate .



Methyl-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-2-methylbenzoate (from Step 1) (42.0 g, 154 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (19.7 ml, 154 mmol) and K_2CO_3 (31.8 g, 231 mmol) in 250 ml of *N,N*-dimethylformamide. After stirring overnight, the reaction was poured into 1 L of cold water. The solution was extracted 3 times with ethyl acetate and the organic layers were dried over $MgSO_4$, and evaporated. The product was carried on to the next step as a crude oil (60.4 g, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.85, 1.28 Hz, 1H), 7.45 - 7.34 (m, 2H), 7.27 - 7.23 (m, 1H), 6.94 - 6.84 (m, 2H), 5.98 (d, J = 2.68 Hz, 1H), 5.92 (dd, J = 2.69, 0.81 Hz, 1H), 5.01 (s, 2H), 3.88 (s, 3H), 2.28 (s, 3H), 1.81 (s, 3H); LC/MS, t_r = 2.96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 400 (M+H). ES-HRMS m/z 400.1341 (M+H calcd for $C_{22}H_{19}F_2NO_4$ requires 400.1355).

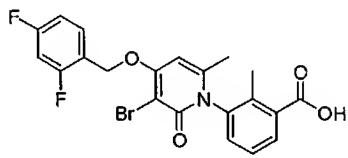
Step 3: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid .



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoate (from Step 2) (60.0 mg, 150 mmol) was stirred with 2.5 N NaOH (120 ml, 300 mmol) in 375 ml of tetrahydrofuran and 75 ml of water at room temperature overnight. The reaction was acidified with 1 N HCl, 350 ml of water was added and the solution was extracted 3 times with ethyl acetate. The combined organic layers were dried over

$MgSO_4$, filtered and evaporated. The resulting solid was filtered, washed with ethyl acetate and dried *in vacuo* to yield a white solid 33.8 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.92, 1.20 Hz, 1H), 7.43 (*app* q, J = 7.70 Hz, 1H), 7.38 (t, J = 7.72 Hz, 1H), 7.35 (dd, J = 7.81, 1.21 Hz, 1H), 6.92 - 6.84 (m, 2H), 6.17 (d, J = 2.56 Hz, 1H), 6.00 (dd, J = 2.55, 0.81 Hz, 1H), 5.05 (s, 2H), 2.30 (s, 3H), 1.84 (s, 3H); LC/MS, t_r = 2.61 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 386 (M+H). ES-HR/MS m/z 386.1228 (M+H calcd for $C_{21}H_{17}F_2NO_4$ requires 386.1198).

Step 4: Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid .



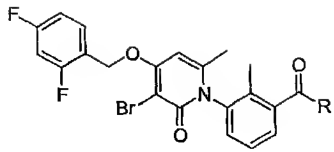
3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (from Step 3) (23.0 g, 59.7 mmol) was stirred at room temperature with *N*-bromosuccinimide (12.74 g, 71.6 mmol) in 120 ml of CH_2Cl_2 for 2 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in acetonitrile for 1 hour, washed 7 times with acetonitrile and dried *in vacuo* to yield a white solid (19.14 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (dd, J = 7.52, 1.61 Hz, 1H), 7.67 (*app* q, J = 7.92 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.33 (dt, J = 9.87, 2.54 Hz, 1H), 7.17 (dt, J = 8.50, 1.67 Hz, 1H), 6.71 (s, 1H), 5.32 (s, 2H), 2.08 (s, 3H), 1.86 (s, 3H);

LC/MS, t_r = 2.69 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 464 (M+H). ES-HRMS *m/z* 464.0284 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464.0304).

Step 5: Preparation of the title compound . 3-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (from Step 4 above) (500 mg, 1.08 mmol) was dissolved in 5 ml of CH_2Cl_2. 4-(2-Aminoethyl)morpholine (170 µl, 1.29 mmol) was added, followed, in order, by EDCI (247 mg, 1.29 mmol), 1-hydroxybenzotriazole (174 mg, 1.29 mmol) and triethylamine (301 µl, 2.16 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and evaporated. The resulting oil was triturated with diethyl ether/hexane to obtain a solid, which was dried *in vacuo* to give a white solid (472 mg, 76%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.64 (*app* q, *J* = 7.79 Hz, 1H), 7.47 (dd, *J* = 7.65, 1.01 Hz, 1H), 7.39 (t, *J* = 7.75 Hz, 1H), 7.17 (dd, *J* = 7.65, 0.81 Hz, 1H), 7.01 (dt, *J* = 8.26, 1.61 Hz, 1H), 6.91 (dt, *J* = 9.42, 2.32 Hz, 1H), 6.49 (t, *J* = 5.04 Hz, 1H), 6.18 (s, 1H), 5.30 (s, 2H), 3.73 (t, *J* = 4.53 Hz, 4H), 3.68 - 3.47 (m, 2H), 2.59 (t, *J* = 5.94 Hz, 2H), 2.51 (t, *J* = 4.33 Hz, 4H), 2.15 (s, 3H), 1.98 (s, 3H); LC/MS, t_r = 2.27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 576 (M+H). ES-HRMS *m/z* 576.1313 (M+H calcd for $C_{27}H_{28}BrF_2N_3O_4$ requires 576.1304).

Examples 329-337

The following compounds are prepared essentially according to the procedure set forth for Example 328:



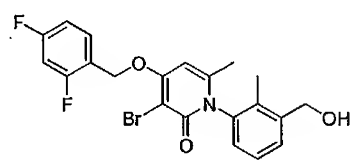
Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 329	$-NHCH_2CH_2OCH_3$	$C_{24}H_{22}BrF_2N_2O_4$	521.0882	521.0906
Ex. 330	$-N(CH_3)_2$	$C_{23}H_{20}BrF_2N_2O_3$	491.0776	491.0752
Ex. 331	$-NHCH_2CH_2OH$	$C_{23}H_{20}BrF_2N_2O_4$	507.0726	507.0689
Ex. 332	$-NHCH_3$	$C_{22}H_{18}BrF_2N_2O_3$	477.0620	477.0585
Ex. 333	$-N(CH_3)CH_2CH_2OH$	$C_{24}H_{22}BrF_2N_2O_4$	521.0882	521.0890
Ex. 334	4-methylpiperazin-1-yl	$C_{26}H_{25}BrF_2N_3O_3$	546.1198	546.1187
Ex. 335	morpholin-4-yl	$C_{25}H_{22}BrF_2N_2O_4$	533.0882	533.0856
Ex. 336	$-N(CH_3)CH_2CH_2OCH_3$	$C_{25}H_{24}BrF_2N_2O_4$	535.1039	535.1055
Ex. 337	$-NH_2$	$C_{21}H_{16}BrF_2N_2O_3$	463.0463	463.0492

NMR characterization of compounds of Examples 329-337

Example No.	NMR Data
Ex. 329	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (*app* q, *J* = 7.79 Hz, 1H), 7.47 (dd, *J* = 7.65, 1.08 Hz, 1H), 7.34 (t, *J* = 7.72 Hz, 1H), 7.12 (dd, *J* = 7.78, 0.94 Hz, 1H), 6.96 (*app* dt, *J* = 7.92, 2.27 Hz, 1H), 6.87 (dt, *J* = 9.46, 2.55 Hz, 1H), 6.29 (m, 1H), 6.12 (s, 1H), 5.25 (s, 2H), 3.73 – 3.65 (m, 1H), 3.56 – 3.48 (m, 3H), 3.35 (d, *J* = 3.09 Hz, 3H), 2.09 (s, 3H), 1.93 (s, 3H)
Ex. 330	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (*app* q, *J* = 7.79 Hz, 1H), 7.34 (t, *J* = 7.66 Hz, 1H), 7.28 (dd, *J* = 7.66, 1.21 Hz, 1H), 7.07 (dd, *J* = 7.65, 1.08 Hz, 1H), 6.96 (*app* dt, *J* = 8.52, 2.02 Hz, 1H), 6.87 (dt, *J* = 9.46, 2.55 Hz, 1H), 6.29 (m, 1H), 6.12 (s, 1H), 5.25 (s, 2H), 3.11 (s, 3H), 2.82 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H)
Ex. 331	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (*app* q, *J* = 7.74 Hz, 1H), 7.46 (d, *J* = 6.71 Hz, 1H), 7.32 (t, *J* = 7.72 Hz, 1H), 7.07 (d, *J* = 6.85 Hz, 1H), 6.98 (m, 2H), 6.87 (dt, *J* = 9.47, 2.41 Hz, 1H),

	6.15 (s, 1H), 5.26 (s, 2H), 3.71 (t, J = 4.97 Hz, 2H), 3.60 - 3.45 (m, 2H), 2.06 (s, 3H), 1.95 (s, 3H)
Ex. 332	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (*app* q, J = 7.79 Hz, 1H), 7.42 (dd, J = 7.66, 0.94 Hz, 1H), 7.31 (t, J = 7.72 Hz, 1H), 7.09 (dd, J = 7.79, 0.94 Hz, 1H), 6.96 (*app* dt, J = 8.26, 1.61 Hz, 1H), 6.87 (dt, J = 9.44, 2.49 Hz, 1H), 6.12 (s, 1H), 5.25 (s, 2H), 2.96 (d, J = 4.83 Hz, 3H), 2.07 (s, 3H), 1.93 (s, 3H)
Ex. 333	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (q, J = 7.92 Hz, 1H), 7.44 - 7.20 (m, 5H), 6.75 (s, 1H), 5.37 (s, 2H), 4.83 (br s, 1H), 3.65 (br s, 2H), 3.45 - 3.33 (m, 2H), 2.81 (s, 3H), 1.93 (d, J = 3.42 Hz, 3H), 1.85 (d, J = 8.06 Hz, 3H)
Ex. 334	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (*app* q, J = 7.92 Hz, 1H), 7.40 (t, J = 7.78 Hz, 1H), 7.34 (dt, J = 9.87, 2.55 Hz, 1H), 7.27 (d, J = 7.52 Hz, 1H), 7.24 (d, J = 7.79 Hz, 1H), 7.17 (dt, J = 8.41, 1.97 Hz, 1H), 6.71 (s, 1H), 5.32 (s, 2H), 3.63 (m, 2H), 3.29 (br s, 1H), 3.09 (br s, 2H), 2.34 (t, J = 4.57 Hz, 2H), 2.20 (br s, 2H), 2.16 (s, 3H), 1.88 (d, J = 8.86 Hz, 3H), 1.80 (d, J = 4.83 Hz, 3H)
Ex. 335	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (*app* q, J = 7.79 Hz, 1H), 7.42 (t, J = 7.65 Hz, 1H), 7.33 (d, J = 7.66 Hz, 1H), 7.14 (d, J = 7.65 Hz, 1H), 7.00 (dt, J = 8.76, 2.21 Hz, 1H), 6.91 (dt, J = 9.47, 2.42 Hz, 1H), 6.17 (s, 1H), 5.29 (s, 2H), 3.98 - 3.92 (m, 1H), 3.80 - 3.77 (m, 3H), 3.59 (br s, 2H), 3.29 (t, J = 4.43 Hz, 2H), 2.04 (s, 3H), 2.00 (s, 3H)
Ex. 336	^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (*app* q, J = 7.79 Hz, 1H), 7.43 - 7.32 (m, 2H), 7.12 (dd, J = 7.66, 1.21 Hz, 1H), 7.00 (dt, J = 9.06, 1.51 Hz, 1H), 6.92 (dt, J = 9.42, 2.52 Hz, 1H), 6.16 (s, 1H), 5.30 (s, 2H), 3.69 (t, J = 5.04 Hz, 2H), 3.39 (s, 3H), 3.26 (s, 1H), 3.19 (s, 1H), 2.91 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H)
Ex. 337	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (br s, 1H), 7.73 (*app* q, J = 7.85 Hz, 1H), 7.53 - 7.20 (m, 5H), 6.74 (s, 1H), 5.37 (s, 2H), 1.99 (s, 3H), 1.92 (s, 3H)

Example 338

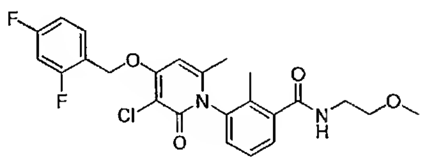


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

3-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 4 above) (2.0 g, 4.31

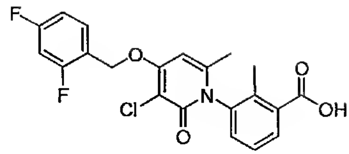
mmol) was cooled to 0°C in 10 ml of tetrahydrofuran. 19.5 ml of 1M $BH_3 \cdot THF$ in tetrahydrofuran was added and stirred overnight, allowing the temperature to rise to room temperature. The reaction was cooled back down to 0°C and ice chips were added to quench the reaction. The slurry was extracted 3 times with an ethyl acetate/tetrahydrofuran mixture. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to give a white solid (1.73 g, 89%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.67 (*app* q, J = 7.92 Hz, 1H), 7.46 (d, J = 7.52 Hz, 1H), 7.32 (dt, J = 10.74, 2.42 Hz, 1H), 7.30 (t, J = 7.72 Hz, 1H), 7.17 (dt, J = 8.46, 1.88 Hz, 1H), 7.03 (d, J = 7.38 Hz, 1H), 6.68 (s, 1H), 5.32 (s, 2H), 4.51 (s, 2H), 3.29 (d, J = 9.40 Hz, 1H), 1.85 (s, 3H), 1.81 (s, 3H), LC/MS, t_r = 2.64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 450 (M+H). ES-HRMS *m/z* 450.0480 (M+H calcd for $C_{21}H_{18}BrF_2NO_3$ requires 450.0511).

Example 339



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-methoxyethyl)-2-methylbenzamide

Step 1: Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid .

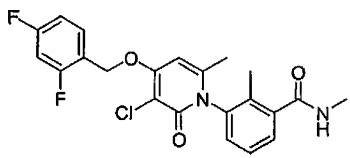


3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 3 above) (10.0 g, 25.9 mmol) was refluxed with *N*-chlorosuccinimide (4.15 g, 31.1 mmol) and dichloroacetic acid (1.06 ml, 12.9 mmol) in 50 ml of CH_2Cl_2 overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in acetonitrile for 30 minutes, washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (8.3 g, 78%). ^1H NMR (300 MHz, DMSO-d_6) δ 7.93 (dd, J = 7.15, 1.92 Hz, 1H), 7.72 (*app* q, J = 7.92 Hz, 1H), 7.52 - 7.35 (m, 3H), 7.22 (dt, J = 8.47, 2.01 Hz, 1H), 6.80 (s, 1H), 5.38 (s, 2H), 2.14 (s, 3H), 1.93 (s, 3H); LC/MS, t_r = 2.64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 420 (M+H). ES-HRMS *m/z* 420.0806 (M+H calcd for $C_{21}H_{16}ClF_2NO_4$ requires 420.0809).

Step 5: Preparation of the title compound . 3-[3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (from Step 1 above) (500 mg, 1.19 mmol) was dissolved in 5 ml of CH_2Cl_2. 2-Methoxyethylamine (129 µl, 1.49 mmol) was added, followed, in order, by EDCI (286 mg, 1.49 mmol), 1-hydroxybenzotriazole (202 mg, 1.49 mmol) and triethylamine (332 µl, 2.38 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and evaporated. The resulting solid was dried *in vacuo* to give a white solid (401 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (*app* q, J = 7.74 Hz,

1H), 7.47 (d, J = 6.98 Hz, 1H), 7.34 (t, J = 7.72 Hz, 1H), 7.11 (d, J = 7.25 Hz, 1H), 6.95 (dt, J = 8.23, 1.66 Hz, 1H), 6.87 (dt, J = 9.51, 2.46 Hz, 1H), 6.35 (br s, 1H), 6.15 (s, 1H), 5.25 (s, 2H), 3.72 - 3.63 (m, 1H), 3.58 - 3.49 (m, 3H), 3.35 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H); LC/MS, t_r = 2.56 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 477 (M+H). ES-HRMS m/z 477.1363 (M+H calcd for $C_{24}H_{23}ClF_2N_2O_4$ requires 477.1387).

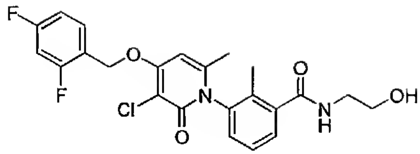
Example 340



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,2-dimethylbenzamide

The title compound was prepared by a procedure similar to the one described for Example 337, where methylamine was used as the amine and the product was obtained in 73% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (*app* d, J = 4.64 Hz, 1H), 7.72 (*app* q, J = 7.92 Hz, 1H), 7.44 - 7.35 (m, 4H), 7.22 (dt, J = 8.54, 1.61 Hz, 1H), 6.78 (s, 1H), 5.37 (s, 2H), 2.79 (d, J = 4.43 Hz, 3H), 1.95 (s, 3H), 1.94 (s, 3H); LC/MS, t_r = 2.46 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 433 (M+H). ES-HRMS m/z 433.1163 (M+H calcd for $C_{22}H_{19}ClF_2N_2O_3$ requires 433.1125).

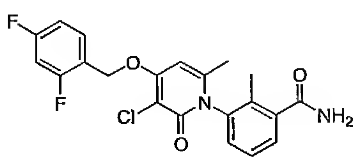
Example 341



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-2-methylbenzamide

The title compound was prepared by a procedure similar to the one described for , where ethanolamine was used as the amine and the product was obtained in 65% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (t, J = 5.51 Hz, 1H), 7.67 (*app* q, J = 7.88 Hz, 1H), 7.43 - 7.33 (m, 3H), 7.23 (d, J = 7.25 Hz, 1H), 7.17 (dt, J = 8.39, 1.66 Hz, 1H), 6.74 (s, 1H), 5.32 (s, 2H), 3.48 (br s, 2H), 3.31 - 3.26 (m, 2H), 1.90 (s, 3H), 1.89 (s, 3H); LC/MS, t_r = 2.34 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 463 (M+H). ES-HRMS m/z 463.1220 (M+H calcd for $C_{23}H_{21}ClF_2N_2O_4$ requires 463.1231).

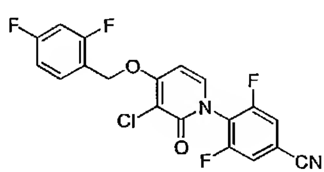
Example 342



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzamide

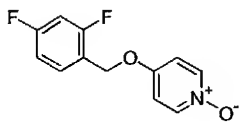
3-[3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 1 above) (500 mg, 1.19 mmol) was stirred with 2-chloro-4,6-dimethoxy-1,3,5-triazine (251 mg, 1.43 mmol) and *N*-methylmorpholine (392 µl, 3.57 mmol) in 5 ml of tetrahydrofuran at room temperature for 2 hours. 2.5 ml of NH_4OH was added and stirred at room temperature for 2.5 hours. The reaction was diluted with tetrahydrofuran and ethyl acetate and extracted. The combined organic layers were washed with $NaHCO_3$, 1 N HCl, and brine, dried over $MgSO_4$, filtered and evaporated. The resulting solid was dried *in vacuo* to obtain a white solid (313 mg, 63%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.87 (br s, 1H), 7.66 (q, J = 7.83 Hz, 1H), 7.48 - 7.30 (m, 3H), 7.23 (d, J = 7.52 Hz, 1H), 7.17 (t, J = 7.65 Hz, 1H), 6.73 (s, 1H), 5.32 (s, 2H), 1.94 (s, 3H), 1.88 (s, 3H); LC/MS, t_r = 2.44 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 419 (M+H). ES-HRMS m/z 419.0963 (M+H calcd for $C_{21}H_{17}ClF_2N_2O_3$ requires 419.0969).

Example 343



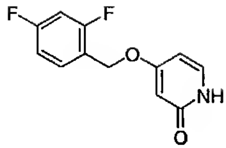
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]pyridine 1-oxide .



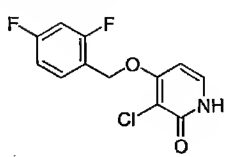
2, 4-difluorobenzyl alcohol (100. g, 0.694 mol) and 4-nitropyridine N-oxide (98. g, 0.700 mol)are combined with 250 g Cs_2CO_3 (1.1 eq) in 2.5 L anhydrous dimethylformamide and heated to 80°C with stirring. The reaction was followed by ^{19}F-NMR (crude reaction mixture with external D_2O reference) and complete after 40 h. The mixture was filtered hot; product crystallized out on cooling. 90.21 g (55%) of white plates were collected by filtration and washed with diethyl ether. The mother liquor was diluted with 2.5 L diethyl ether and stored in the freezer overnight, yielding a second crop 68.76 g (41%, combined yield 96%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.06 (m, 2 H), 7.61 (quartet, J = 8.45 Hz, 1H), 7.30 (t, J = 10.37 Hz,1H), 7.12, (t, J = 8.45 Hz, 1H), 7.09 (d, J = 5.06 Hz, 2H), 5.14 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.43 (quintet, J = 7.78 Hz, 1F), -113.82 (quartet, J = 9.55 Hz, 1F). LC/MS t_r = 3.90 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 238 (M+H).

Step 2: Preparation of 4-[(2,4-difluorobenzyl)oxy]-pyridin-2(1H)-one (7).



4-[(2,4-difluorobenzyl)oxy]pyridine 1-oxide (from Step 1) (30.0 g , 0.127 mol), anhydrous potassium acetate (25 g, 0.25 mol), acetic anhydride (25 g, 0.25 mol), and 10 ml acetic acid were combined in a 250-ml round-bottomed flask with overhead stirring and heated to 130°C for 4 hours. The mixture was concentrated under vacuum, the solids dissolved in 95 ml acetonitrile: 5 ml water, filtered through charcoal and poured into 600 ml ice with stirring. The mixture was allowed to stand overnight at room temperature, then 9.62 g (30%) product collected by filtration as a medium brown solid (adequate for the next step without purification). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.59 (quartet, J = 9.91 Hz, 1H), 7.29 (t, J = 10.36 Hz, 1H), 7.21 (d, J = 8.20 Hz, 1H), 7.11 (t, J = 8.48 Hz, 1H), 5.83 (m, 2H), 5.02 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.57(quintet, J = 7.66 Hz, 1F) -113.88 (quartet, J = 8.93 Hz, 1F). LC/MS t_r = 4.29 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 254 nm, at 50°C) ES-MS m/z 238 (M+H).

Step 3: Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one .



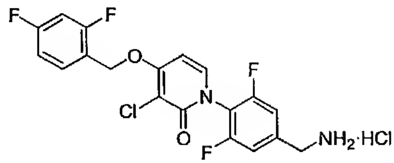
4-[(2,4-difluorobenzyl)oxy]-pyridin-2(1H)-one (from Step 2) (8.60 g, 36.3 mmol) was stirred in 150 ml dimethylformamide and treated with N-chlorosuccinimide (5.4 g, 39.9 mmol). After 15 hours, the precipitate was collected by filtration (5.11 g, 52%) yeilding a lustrous white solid. The mother liquor was diluted to 500 ml with diethyl ether, providing 2.47 g (25%) in a second crop. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.60 (quartet, J = 6.34 Hz, 1H), 7.43 (d, J = 7.58 Hz, 1H), 7.31 (dt, J = 10.08, 2.21 Hz, 1H), 7.14 (dt, J = 8.65, 1.79 Hz, 1H), 6.44 (d, J = 7.49 Hz, 1H), 5.28 (s, 1H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.58 (quintet, J = 7.75 Hz, 1F), -113.68 (quartet, J = 8.68 Hz, 1F). LC/MS t_r = 4.47 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 254 nm, at 50°C) ES-MS m/z 272, 274 3:1 (M+H).

Step 4: Preparation of the title compound .

3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (from step 3) (3.25 g, 11.9 mmol) was combined with Cs_2CO_3 (3.93 g, 12.1 mmol) in 50 ml dimethylformamide and heated to 70°C, stirring under nitrogen. 3,4,5-trifluorobenzonitrile (1.83 g, 11.9 mmol) was added. After 4 hours, the mixture was filtered, concentrated *in vacuo*, washed thrice with hot cyclohexane, dissolved in tetrahydrofuran, treated with $MgSO_4$ and charcoal, and filtered. The solution was evaporated leaving a fine white solid (3.99 g, 82%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 7.59 Hz, 2H), 7.92 (d, J = 8.31 Hz, 1H), 7.65 (quartet, J = 6.77, 1H), 7.34 (dt, J = 9.81, 2.71 Hz, 1H), 7.16 (dt, J = 8.59, 2.50 Hz, 1H), 6.87 (d, J = 8.01 Hz, 1H), 5.39 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.17 (quintet, J = 8.97 Hz, 1F), -113.51(quartet, J = 9.53 Hz, 1F), -116.32 (d, J = 7.69 Hz, 2F). LC/MS t_r = 5.51 minutes (0-

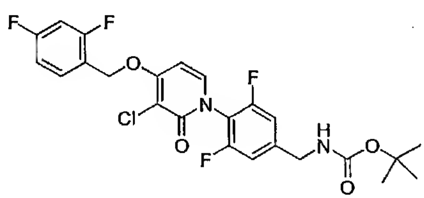
95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 409 (M+H). ES-HRMS *m/z* 409.0351 (M+H calcd for $C_{19}H_{10}ClF_4N_2O_2$ requires 409.0361).

Example 344



1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride

Step 1: Preparation of tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate .



4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (2.84 g, 6.95 mmol), di-*t*-butyl-dicarbonate (3.18 g, 14.6 mmol), and nickel(II) chloride (0.90 g, 6.95 mmol) were combined with 40 ml methanol and 40 ml tetrahydrofuran and cooled to 0°C stirring in an ice bath. Sodium borohydride (1.33 g, 35.2 mmol) was added in small

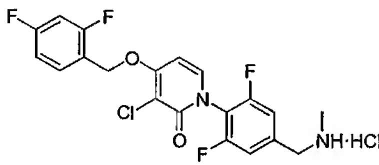
portions over 10 minutes to control foaming, and the reaction was stirred 1 hour. Additional sodium borohydride (0.50 g, 13.2 mmol) was required to force the reaction to completion by LC. A color change from yellow to black persisted on completion. The mixture was filtered through a bed of charcoal layered on anhydrous $MgSO_4$ and evaporated to dryness. Excess di-*t*-butyl-dicarbonate and byproduct *t*-butanol were removed by repeated heating with water to 80°C *in vacuo*, giving the product as a fine white powder (3.11 g, 87%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.89 (d, *J* = 8.04 Hz, 1H), 7.65 (quartet, *J* = 6.73 Hz, 1H), 7.55 (t, *J* = 6.73 Hz,1H), 7.34, (dt, *J* = 10.05, 2.51 Hz, 1H), 7.16 (m, 3H), 6.77 (d, *J* = 8.18 Hz, 1H), 5.34 (s, 2H), 4.18 (d, *J* = 5.68 Hz, 2H), 1.34 (s, 9H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.26 (quintet, *J* = 6.91 Hz, 1F), -113.53 (quartet, *J* = 7.73 Hz, 1F), -120.32(d, *J* = 8.91 Hz, 2F). LC/MS t_r = 5.90 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 513 (M+H). ES-HRMS *m/z* 513.1164 (M+H calcd for $C_{24}H_{22}ClF_4N_2O_4$ requires 513.1199).

Step 2: Preparation of the title compound .

tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate (from step 3) (1.39 g, 2.71 mmol) was dissolved in 20 ml tetrahydrofuran and treated with 4 ml concentrated hydrochloric acid. The solution was evaporated and dried *in vacuo* to a fine white solid (1.20 g, 99%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.54 (m, 2H), 7.86 (d, *J* = 7.57 Hz, 1H), 7.65 (quartet, *J* = 7.62, 1H), 7.50 (d, *J* = 9.25 Hz, 2H), 7.34 (dt, *J* = 10.50, 2.45 Hz, 1H), 7.16 (dt, *J* = 8.38, 2.55 Hz, 1H), 6.78 (d, *J* = 7.86 Hz, 1H), 5.37 (s, 2H), 4.10 (br s, 2H), 4.97-3.14 (v br s, 3H). ^{19}F-NMR

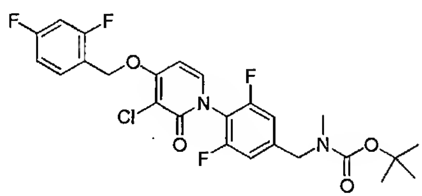
(400 MHz, DMSO-d_6) δ -109.21 (quintet, J = 7.77 Hz, 1F), -113.51(quartet, J = 8.95 Hz, 1F), -119.56 (d, J = 9.44 Hz, 2F). LC/MS t_r = 4.33 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 413 (M+H). ES-HRMS m/z 413.0712 (M+H calcd for $C_{19}H_{14}ClF_4N_2O_2$ requires 413.0674).

Example 345



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(methylamino)methyl]phenyl}pyridin-2(1H)-one hydrochloride

Step 1: Preparation of tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(methyl)carbamate .



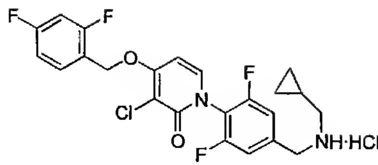
tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate (from Step 1) (252 mg, 0.491 mmol) and iodomethane (75 mg, 0.528 mmol) are combined in 8 ml anhydrous dimethylformamide. Sodium hydride 60% in mineral oil (30 mg, 0.75 mmol) was added and

the mixture stirred under nitrogen at room temperaure for 1 hour. Saturated aqueous NH_4Cl was added (4 ml) followed by 20 ml water and the product was extracted into ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the product as a white powder (208 mg, 80%). ^1H-NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 7.85 Hz, 1H), 7.64 (quartet, J = 6.66 Hz, 1H), 7.32, (dt, J = 9.39, 3.29 Hz, 1H), 7.13 (m, 3H), 6.77 (d, J = 7.94 Hz, 1), 5.38 (s, 2H), 4.43 (s, 2H), 2.90 (s, 3H), 1.40 (br m, 9H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.25 (quintet, J = 8.93 Hz, 1F), -113.53 (quartet, J = 9.73 Hz, 1F), -119.89(d, J = 9.35 Hz, 2F). LC/MS t_r = 6.16 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 527 (M+H). ES-HRMS m/z 527.1338 (M+H calcd for $C_{25}H_{24}ClF_4N_2O_4$ requires 527.1355).

Step 2: Preparation of the title compound .

tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(methyl)carbamate (from step 1) (188 mg, 0.357 mmol) was subjected to the conditions of Step 2, yielding a fine white solid (165 mg, 100%). ^1H-NMR (400 MHz, DMSO-d_6) δ 9.30 (br s, 2H), 7.89 (d, J = 7.99 Hz, 1H), 7.65 (quartet, J = 7.64, 1H), 7.55 (d, J = 8.66 Hz, 2H), 7.34 (dt, J = 9.93, 2.57 Hz, 1H), 7.17 (dt, J = 8.49, 2.48 Hz, 1H), 6.81 (d, J = 8.01 Hz, 1H), 5.39 (s, 2H), 4.21 (s, 2H), 2.56 (s, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.20 (quintet, J = 7.56 Hz, 1F), -113.52(quartet, J = 9.67 Hz, 1F), -119.21 (d, J = 8.79 Hz, 2F). LC/MS t_r = 4.30 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 427 (M+H). ES-HRMS m/z 427.0816 (M+H calcd for $C_{20}H_{16}ClF_4N_2O_2$ requires 427.0831).

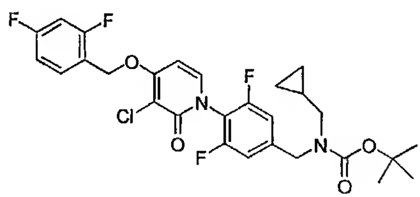
Example 346



3-chloro-1-(4-{[(cyclopropylmethyl)amino]methyl}-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride

The title compound was prepared by direct analogy with , replacing iodomethane with bromocyclopropylmethane and extending the reaction time to 6 hours in Step 1.

Step 1:



1 tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(cyclopropylmethyl)carbamate

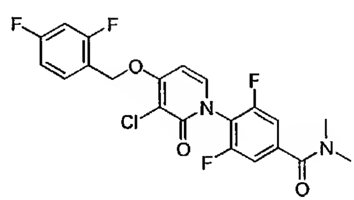
^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.91 Hz, 1H), 7.65 (quartet, J = 6.81 Hz, 1H), 7.33, (dt, J = 9.90, 2.26 Hz, 1H), 7.17 (m, 3H), 6.77 (d, J = 7.90 Hz, 1), 5.38 (s, 2H), 4.51 (s, 2H), 3.10 (br s, 2H), 1.36 (m, 9H), 0.97 (br s, 1H), 0.38 (m, 2H), 0.18 (m, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.25

(quintet, J = 7.77 Hz, 1F), -113.54 (quartet, J = 9.02 Hz, 1F), -120.24(m, 2F). LC/MS t_r = 5.99 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 567 (M+H). ES-HRMS m/z 567.1653 (M+H calcd for $C_{28}H_{28}ClF_4N_2O_4$ requires 567.1668).

Step 2: Title compound .

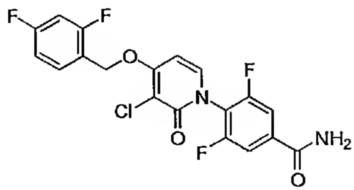
^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.51 (br s, 2H), 7.87 (d, J = 7.96 Hz, 1H), 7.63 (m, 3H), 7.33 (dt, J = 9.93, 2.65 Hz, 1H), 7.16 (dt, J = 8.36, 2.32 Hz, 1H), 6.81 (d, J = 7.92 Hz, 1H), 5.38 (s, 2H), 4.22 (br s, 2H), 2.82 (br s, 2H), 1.10 (m, 1H), 0.57 (m, 2H), 0.36 (m, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.25 (quintet, J = 7.69 Hz, 1F), -113.54(quartet, J = 9.35 Hz, 1F), -120.24 (m, 2F). LC/MS t_r = 4.55 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 467 (M+H). ES-HRMS m/z 467.1119 (M+H calcd for $C_{23}H_{20}ClF_4N_2O_2$ requires 467.1144).

Example 347



4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluoro-*N*,*N*-dimethylbenzamide

Step 1: Preparation of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzamide .



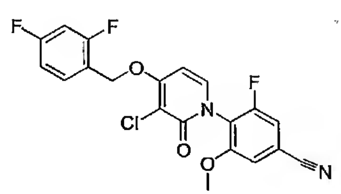
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (540 mg, 1.32 mmol) and potassium trimethylsilonate 90% (375 mg, 2.63 mmol) are combined in 8 ml anhydrous toluene and heated to reflux with stirring. After 10 minutes, the mixture allowed to cool then partitioned between saturated aqueous ammonium chloride and ethyl acetate. The aqueous layer is extracted twice with ethyl acetate, the combined organics are washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The crude product is taken up in tetrahydrofuran and filtered through charcoal layered over silica gel, and the solution evaporated *in vacuo* to give the product as a white powder (468 mg, 83%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.22 (br s, 2H), 7.92 (d, J = 7.84 Hz, 1H), 7.78 (d, J = 8.45, 2H), 7.65 (quartet, J = 8.40 Hz, 1H), 7.34, (dt, J = 10.09, 2.58 Hz, 1H), 7.17 (dt, J = 8.72, 2.30 Hz, 1H), 6.83 (d, J = 7.91 Hz, 1H), 5.39 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.21 (quintet, J = 7.43 Hz, 1F), -113.52 (quartet, J = 9.62 Hz, 1F), -118.74 (d, J = 8.88 Hz, 2F). LC/MS t_r = 4.67 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS m/z 427 (M+H). ES-HRMS m/z 427.0454 (M+H calcd for $C_{19}H_{12}ClF_4N_2O_3$ requires 427.0467).

Step 2: Preparation of the title compound .

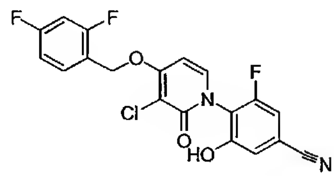
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzamide (from step 1) (243 mg, 0.357 mmol) was subjected to the conditions of Step 1, with the exception that two equivalents of sodium hydride 60% in mineral oil and iodomethane were used instead of one (46 mg, 0.69 mmol and 103 mg, 0.724 mmol respectively). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 7.76 Hz, 1H), 7.66 (quartet, J = 7.33, 1H), 7.44 (d, J = 7.59 Hz, 2H), 7.34 (dt, J = 9.88, 2.63 Hz, 1H), 7.17 (dt, J = 8.35, 2.06 Hz, 1H), 6.83 (d, J = 7.55 Hz, 1H), 5.39 (s, 2H), 2.98 (s, 3H), 2.91 (s, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.22 (quintet, J = 8.10 Hz, 1F), -113.53(quartet, J = 9.18 Hz, 1F), -118.88 (d, J = 7.77 Hz, 2F). LC/MS t_r = 5.13 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 455 (M+H). ES-HRMS m/z 455.0791 (M+H calcd for $C_{21}H_{16}ClF_4N_2O_3$ requires 455.0780).

Example 348



4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-methoxybenzonitrile

Step 1: Preparation of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-hydroxybenzonitrile .



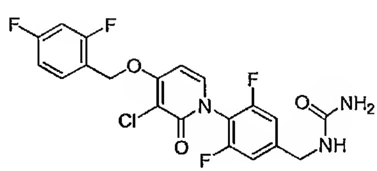
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (522 mg, 1.28 mmol) and potassium trimethylsilonate 90% (655 mg, 4.60 mmol) are combined in 8 ml anhydrous tetrahydrofuran and stirred under nitrogen at room temperature for 2 hours. The precipitated potassium salt of was collected by filtration, washed with a minimum of tetrahydofuran, and dried *in vacuo*. A portion of this salt (275 mg, 0.618 mmol) was dissolved in 5 ml water, the pH was adjusted below 6 with concentrated hydrochloric acid, the product collected by filtration, washed with water, sucked dry under a blanket of dry nitrogen, and dried further *in vacuo* overnight (251 mg, 100%, 98% overall). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.46 (br s, 1H), 7.74 (d, J = 7.81 Hz, 1H), 7.67 (quartet, J = 6.76 Hz, 1H), 7.52 (d, J = 8.76, 1H), 7.364, (dt, J = 10.18, 2.37 Hz, 1H), 7.24 (br s, 1H), 7.17 (br t, J = 8.75, 1H), 6.74 (d, J = 8.04 Hz, 1H), 5.39 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.26 (quintet, J = 8.50 Hz, 1F), -113.52 (quartet, J = 9.29 Hz, 1F), -118.06 (d, J = 9.38 Hz, 1F). LC/MS t_r = 5.13 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS *m/z* 407 (M+H). ES-HRMS *m/z* 407.0381 (M+H calcd for $C_{19}H_{11}ClF_3N_2O_3$ requires 407.0405).

Step 2: Preparation of the title compound.

The potassium salt of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-hydroxybenzonitrile (from Step 1) (273 mg, 0.614 mmol) was stirred in 5 ml anhydrous dimethylformamide under nitrogen. Iodomethane (93 mg, 0.66 mmol) was added, and stirring continued for 2 hr. The mixture was diluted to 50 ml with ice-cold water, and the white precipitate collected by filtration. The precipitate was washed thrice with water, sucked dry under a blanket of nitrogen, and dried further *in vacuo* overnight (242 mg, 87%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.73 (m, 2H), 7.65 (m, 2H), 7.34 (dt, J = 9.90, 2.39 Hz, 1H), 7.17 (dt, J = 8.75, 2.47 Hz, 1H), 6.75 (d, J = 7.97 Hz, 1H), 5.37 (s, 2H), 3.84 (s, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.24 (quintet, J = 7.85 Hz, 1F), -113.54 (quartet, J = 9.83 Hz, 1F), -118.33 (d, J = 7.77 Hz, 1F). LC/MS t_r = 5.40 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 421 (M+H). ES-HRMS *m/z* 421.0522 (M+H calcd for $C_{20}H_{13}ClF_3N_2O_3$ requires 421.0561).

Example 349

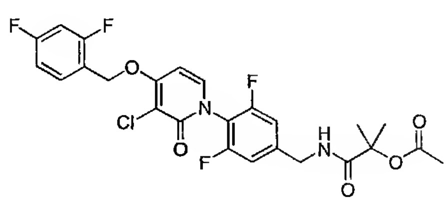


N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}urea

Step 1: Preparation of the title compound

1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (162 mg, 0.361 mmol) is dissolved in 4 ml 50% aqueous acetic acid and treated with potassium cyanate (59 mg, 0.72 mmol). The mixture was stirred 2 hr, then the mixture was diluted to 50 ml with cold water, and the crude product, contaminated with the acetamide, was purified by silica gel chromatography, eluting first with 20% ethanol in hexane then 40% ethanol in hexane. The 50% fractions were pooled by TLC and evaporated, giving the product as a fine white powder (65 mg, 40%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 8.07 Hz, 1H), 7.64 (quartet, J = 6.53 Hz, 1H), 7.33, (dt, J = 9.47, 1.99 Hz, 1H), 7.15 (m, 3H), 6.76 (d, J = 7.97 Hz, 1H), 6.59 (m, 1H), 5.65 (br s, 2H), 5.38 (s, 2H), 4.22 (m, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.22 (quintet, J = 7.86 Hz, 1F), -113.51 (quartet, J = 9.40 1F), -120.65 (d, J = 8.75 Hz, 2). LC/MS t_r = 4.85 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 456 (M+H).

Example 350

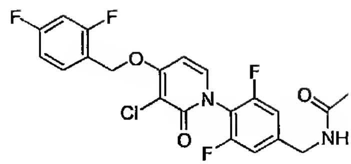


2-({4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}amino)-1,1-dimethyl-2-oxoethyl acetate

Step 1: Preparation of the title compound

1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (225 mg, 0.501 mmol) is dissolved in a solution of 10 ml tetrahydrofuran and triethylamine (111 mg, 1.10 mmol). 2-acetoxy-2-methyl-propionyl chloride (85 mg, 0.516 mmol) is added, and the mixture stirred for 30 minutes before partitioning between saturated aqueous ammoniom chloride and ethyl acetate. The layers are seperated, and the aqueous phase extracted twice with ethyl acetate. The combined organics are washed with water and brine, then dried over $MgSO_4$, filtered, and evaporated in vacuo, giving the product as a fine white powder (254 mg, 94%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.47 (t, J = 6.16 Hz, 1H), 7.88 (d, J = 7.71 Hz, 1H), 7.65 (quartet, J = 7.24 Hz, 1H), 7.34, (dt, J = 10.04, 2.49 Hz, 1H), 7.16 (m, 3H), 6.77 (d, J = 7.78 Hz, 1H), 5.38 (s, 2H), 4.32 (d, J = 5.93 2H), 2.02 (s, 3H), 1.48(s, 6H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.26 (quintet, J = 9.00 Hz, 1F), -113.52 (quartet, J = 9.52 Hz, 1F), -120.62 (d, J = 9.09 Hz, 2F). LC/MS t_r = 5.43 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 541 (M+H). ES-HRMS m/z 541.1128 (M+H calcd for $C_{25}H_{22}ClF_4N_2O_5$ requires 541.1148).

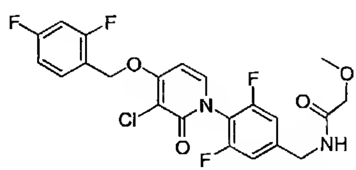
Example 351



N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}acetamide

The compound was prepared in the following the produre for Example 350, substituting acetyl chloride (24 mg, 0.30 mmol) for 2-acetoxy-2-methyl-propionyl chloride. (128 mg, 96%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.48 (br s, 1H), 7.87 (d, *J* = 7.28 Hz, 1H), 7.64 (quartet, *J* = 8.01 Hz, 1H), 7.33, (dt, *J* = 9.87, 2.25 Hz, 1H), 7.17 (m, 3H), 6.76 (d, *J* = 8.25 Hz, 1H), 5.38 (s, 2H), 4.30 (m, 2H), 1.88(s, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.22 (quintet, *J* = 8.04 Hz, 1F), -113.52 (quartet, *J* = 9.91 Hz, 1F), -120.43 (d, *J* = 8.77 Hz, 2F). LC/MS t_r = 5.04 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 555 (M+H). ES-HRMS *m/z* 455.0824 (M+H calcd for $C_{21}H_{16}ClF_4N_2O_3$ requires 455.0780).

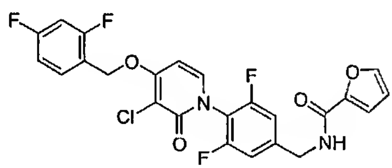
Example 352



N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-methoxyacetamide

The compound was prepared in the following the produre for EXAMPLE 350, substituting 2-methoxy-acetyl chloride (45 mg, 0.415 mmol) for 2-acetoxy-2-methyl-propionyl chloride. (124 mg, 78%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.56 (t, J = 6.77 Hz, 1H), 7.90 (d, J = 7.85 Hz, 1H), 7.67 (quartet, J = 7.67 Hz, 1H), 7.36, (dt, J = 10.03, 2.36 Hz, 1H), 7.20 (m, 3H), 6.79 (d, J = 8.07 Hz, 1H), 5.40 (s, 2H), 4.37 (d, J = 6.28 Hz, 2H), 3.91(s, 2H), 3.35 (s, 3 H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.23 (quintet, J = 8.29 Hz, 1F), -113.50 (quartet, J = 9.36 Hz, 1F), -120.43 (d, J = 9.07 Hz, 2F). LC/MS t_r = 5.13 miinutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 485 (M+H). ES-HRMS m/z 485.0856 (M+H calcd for $C_{22}H_{18}ClF_4N_2O_4$ requires 485.0886).

Example 353

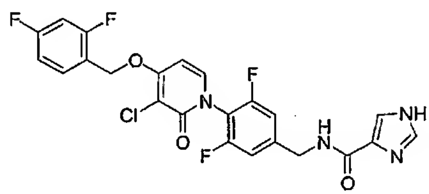


N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-furamide

The compound was prepared in the following the produre for EXAMPLE 350, substituting furoyl chloride (62 mg, 0.48 mmol) for 2-acetoxy-2-methyl-propionyl chloride. Yield: 142 mg, 85%. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.07 (t, J = 6.14 Hz, 1H), 7.90 (d, J = 7.88 Hz, 1H), 7.87 (dd, J = 1.69, 0.80 Hz, 1H), 7.67 (td, J = 8.46, 6.80 Hz, 1H), 7.35, (dt, J = 10.00, 2.81 Hz, 1H), 7.26 (d, J = 8.78 Hz, 2H), 7.18 (ddt, J = 8.58, 2.30, 1.07 Hz,

1H), 7.16 (dd, J = 3.52, 0.77 Hz, 1H), 6.79 (d, J = 8.07 Hz, 1H), 6.64 (dd, J = 3.16, 1.73 Hz, 1H), 5.40 (s, 2H), 4.49 (d, J = 6.13 Hz, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.23 (quintet, J = 7.65 Hz, 1F), -113.50 (quartet, J = 9.84 Hz, 1F), -120.29 (d, J = 9.41 Hz, 2F). LC/MS t_r = 5.32 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 507 (M+H). ES-HRMS m/z 507.0716 (M+H calcd for $C_{24}H_{16}ClF_4N_2O_4$ requires 507.0729).

Example 354



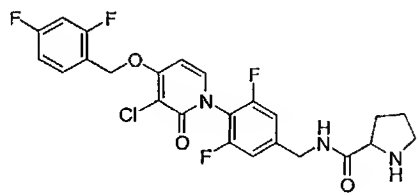
N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-1H-imidazole-4-carboxamide

Step 1: Preparation of the title compound

1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (150 mg, 0.334 mmol) is dissolved in a solution of 4 ml tetrahydrofuran and triethylamine (35 mg, 0.35 mmol). 4-imidazolecarboxylic acid (62 mg, 0.56 mmol), 1-hydroxybenzotriazole hydrate (90 mg, 0.67 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (128 mg, 0.668 mmol), and triethylamine (100. mg, 0.989 mmol) were combined in 5 ml tetrahydrofuran and stirred under nitrogen. The solution containing 1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-

[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride was added in one portion, rinsing with 2 ml tetrahydrofuran. Stirring was continued at room temperature overnight, then the reaction was poured into 90 ml of icewater, and the product collected by filtration and dired *in vacuo* (254 mg, 94%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.55 (br s, 1H), 8.73 (t, J = 6.57 Hz, 1H), 7.90 (d, J = 7.87 Hz, 1H), 7.75 (s, 1H), 7.67 (m, 2H), 7.35, (dt, J = 10.04, 2.54 Hz, 1H), 7.21 (m, 3H), 6.78 (d, J = 8.04 Hz, 1H), 5.39 (s, 2H), 4.47 (m, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.26 (quintet, J = 7.87 Hz, 1F), -113.52 (quartet, J = 9.30 Hz, 1F), -120.59 (d, J = 9.21 Hz, 2F). LC/MS t_r = 4.48 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 507 (M+H). ES-HRMS m/z 507.0818 (M+H calcd for $C_{23}H_{16}ClF_4N_4O_3$ requires 507.0842).

Example 355



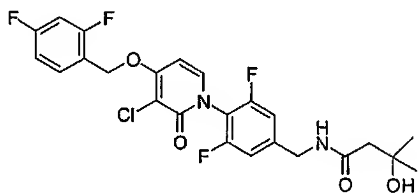
N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-5-oxoprolinamide

Step 1: Preparation of the title compound

The compound was prepared following the procedure for Example 354, substituting 2-pyrrolidone-5-carboxylic acid for 4-imidazolecarboxylic acid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.67 (t,

J = 6.08 Hz, 1H), 7.88 (m, 1H), 7.65 (qr, J = 7.57, 1H), 7.34, (dt, J = 9.32, 2.63 Hz, 1H), 7.22 (d, J = 9.36, 2H), 7.17 (dt, J = 8.51, 2.55 Hz, 1H), 6.77 (d, J = 7.66 Hz, 1H), 5.73 (s, 1H), 5.38 (s, 2H), 4.35 (d, J = 5.74, 2H), 4.05 (m, 1H), 2.15 (m, 2H), 1.90 (m, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.25 (quintet, J = 7.72 Hz, 1F), -113.52 (quartet, J = 8.94 Hz, 1F), -120.39 (d, J = 9.11 Hz, 2F). LC/MS t_r = 4.81 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 524 (M+H). ES-HRMS m/z 524.0998 (M+H calcd for $C_{24}H_{19}ClF_4N_3O_4$ requires 524.0995).

Example 356



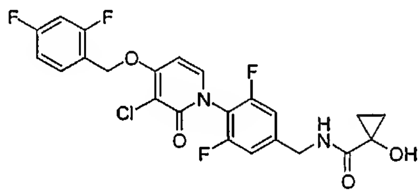
N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-3-hydroxy-3-methylbutanamide

Step 1: Preparation of the title compound

The compound was prepared following the procedure for , substituting 2-hydroxy-2-methyl butyric acid for 4-imidazolecarboxylic acid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.43 (t, J = 6.04 Hz, 1H), 7.88 (d, J = 8.01, 1H), 7.65 (qr, J = 6.84, 1H), 7.34, (dt, J = 10.13, 2.55 Hz, 1H), 7.22 (d, J = 8.74, 2H), 7.16 (dt, J = 8.57, 2.45 Hz, 1H), 6.77 (d, J = 7.89 Hz, 1H), 5.38 (s, 2H), 4.75 (s, 0.5H (O*H*)), 4.35 (d, J = 6.48,

2H), 2.28 (s, 2H), 1.47 (s, 0.5H(O*H*)), 1.16 (s, 6H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.26 (quintet, *J* = 7.79 Hz, 1F), -113.53 (quartet, *J* = 9.23 Hz, 1F), -120.49 (d, *J* = 9.39 Hz, 2F). LC/MS t_r = 5.08 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 513 (M+H). ES-HRMS *m/z* 513.1177 (M+H calcd for $C_{24}H_{22}ClF_4N_2O_4$ requires 513.1199).

Example 357



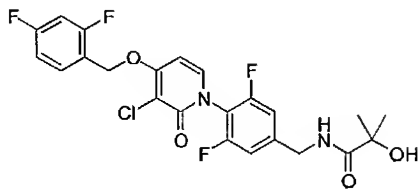
N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-1-hydroxycyclopropanecarboxamide

Step 1: Preparation of the title compound

The compound was prepared following the procedure for , substituting 1-hydroxy-1-cyclopropanecarboxylic acid for 4-imidazolecarboxylic acid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.70 (t, *J* = 6.26 Hz, 1H), 7.89 (d, *J* = 6.31, 1H), 7.65 (qr, *J* = 6.83, 1H), 7.34 (t, *J* = 10.58 Hz, 1H), 7.19 (m, 3H), 6.77 (d, *J* = 7.70 Hz, 1H), 5.38 (s, 2H), 4.35 (d, *J* = 5.66, 2H), 1.14 (s, 1H), 1.02 (m, 2H), 0.84 (m, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.25 (quintet, *J* = 8.05 Hz, 1F), -113.53 (quartet, *J* = 8.27 Hz, 1F), -120.59 (d, *J* = 8.99 Hz, 2F). LC/MS t_r = 5.01 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS m/z 497 (M+H). ES-HRMS m/z 497.0873 (M+H calcd for $C_{23}H_{18}ClF_4N_2O_4$ requires 497.0886).

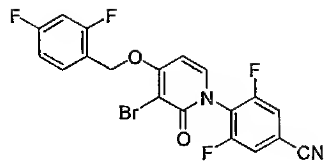
Example 358



N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-hydroxy-2-methylpropanamide

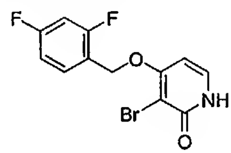
Step 1: Preparation of the title compound
The compound was prepared following the procedure for , substituting 2-hydroxyisobutyric acid for 4-imidazolecarboxylic acid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.48 (t, J = 6.41 Hz, 1H), 7.89 (d, J = 7.78, 1H), 7.65 (qr, J = 9.10, 1H), 7.33 (dt, J = 10.12, 2.41 Hz, 1H), 7.17 (m, 3H), 6.77 (d, J = 7.69 Hz, 1H), 5.38 (s, 2H), 4.31 (d, J = 6.50, 2H), 1.41 (s, 1H), 1.33 (s, 6H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.25 (quintet, J = 7.49 Hz, 1F), -113.53 (quartet, J = 9.64 Hz, 1F), -120.59 (d, J = 8.68 Hz, 2F). LC/MS t_r = 5.05 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 499 (M+H). ES-HRMS m/z 499.1020 (M+H calcd for $C_{23}H_{20}ClF_4N_2O_4$ requires 499.1042).

Example 359



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile

Step 1: Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one .



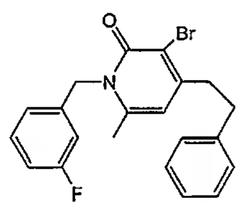
The compound was prepared in the following the produre for 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (, Step 3), substituting *N*-bromosuccinimide for *N*-chlorosuccinimide. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.85 (br s, 1H), 7.61 (m, 1H), 7.46 (d, *J* = 7.36 Hz, 1H), 7.30, (m, 1H), 7.14 (m, 1H), 6.40 (d, *J* = 7.71 Hz, 1H), 5.26 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.69 (quintet, *J* = 7.93 Hz, 1F), -113.63 (quartet, *J* = 9.55 Hz, 1F). LC/MS t_r = 4.48 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 316 (M+H).

Step 2: Preparation of the title compound .

The compound was prepared following the procedure for 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (, Step 4), substituting 3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (from step 1) (1.92 g,

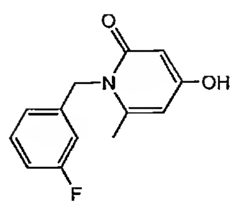
6.06 mmol) for 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (, from Step 3). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 7.24 Hz, 2H), 7.95 (d, J = 7.76 Hz, 1H), 7.66 (quartet, J = 8.71 Hz, 1H), 7.34, (dt, J = 9.94, 2.53 Hz, 1H), 7.17 (dt, J = 8.64, 2.33 Hz, 1H), 6.82 (d, J = 7.77 Hz, 1H), 5.39 (s, 2H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.28 (quintet, J = 7.98 Hz, 1F), -113.45 (quartet, J = 9.29 Hz, 1F), -116.30 (d, J = 7.44 Hz, 2F). LC/MS t_r = 5.48 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 453 (M+H). ES-HRMS m/z 452.9836 (M+H calcd for $C_{19}H_{10}BrF_4N_2O_2$ requires 452.9856).

Example 360



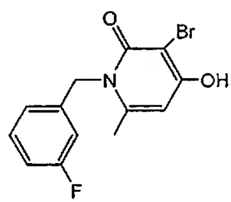
3-Bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one

Step 1: Preparation of 1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one



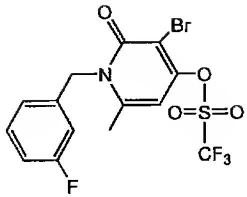
A mixture of 4-hydroxy-6-methyl-2-pyrone (2.5 g, 0.02 mol) and 3-fluorobenzylamine (2.5 g, 0.02 mol) in n-butanol (15 .0 mL) was heated to reflux for 16 h under argon atmosphere. Butanol wad distilled in vacuo, the residue was triturated with EtOAc, cooled and filterd the precipitate. It was washed with cold EtOAc, and dried to give 0.86 g of the title compound as a pale yellow powder: 1H- NMR (CD3OD/400 MHz) δ 7.31 (m, 1H), 7.0 - 6.85 (m, 2H), 6.83 (d, 1H, J = 9.6 Hz), 5.96 (d, 1H, j = 2.0 Hz), 5.80 (d, 1H, J = 2.0 Hz), 5.30 (s, 2H), and 2,24 (s, 3H); ESMS m/z = 234 (MH+).

Step 2: Preparation of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one



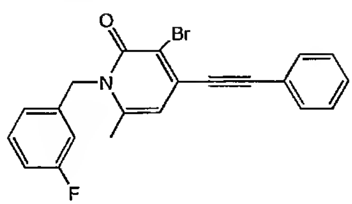
A mixture of 1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.8 g, 0.0034 mol), NBS (0.64 g, 0.0036 mol) in dichloromethane (15.0 mL) was stirred at room temperature, under argon atmosphere. After 1.5 h, the reaction mixture was diluted with dichloromethane (15.0 mL), cooled and filterd the solids. The residue was washed with dichloromethane and dried in vacuo to give 0.93 g of the title compound as a white powder: 1H- NMR (CD3OD/400 MHz) δ . 7.33 (m, 1H), 7.2 - 6.8 (m, 3H), 6.07 (s, 1H), 5.34 (s, 2H), 2.26 (s, 3H); ESHRMS m/z 312.0016 (M+H C13H12NO2BrF requires 312.0035).

Step 3: Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate



To a suspension of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.86 g, 0.0028 mol) in dichloromethane (15.0 mL) cooled to -30 °C, triethyl amine (0.5 mL, 0.004 mol) and trflic anhydride (0.7 mL, 0.0042 mol) were added and stirred for 1 h. The resulting orange solution was poured into ice cold water (25 mL) and extracted with dichloromethane (2 x 25 mL) The combined organic extracts were washed with water, dried (Na2SO4) and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography using 1:1 EtOAc/hexane v/v to afford 1.0 g (85%) the title compound as a light brown solid: ^{1}H- NMR (CDCl3/400 MHz) δ 7.32 (m,1H), 7.0 - 6.85 (m, 3H), 6.18 (s, 1H), 5.32 (s, 2H), and 2.34 (s, 3H); ESHRMS m/z 443.9492 (M+H C14H11NO4BrF4S requires 443.9528).

Step 4: Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one



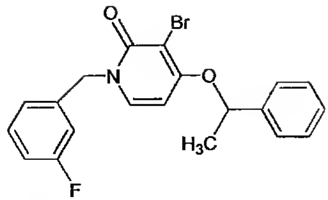
A solution of 3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1.0 g, 0.0022 mol) and phenylacetylene (0.3 mL, 0.0029 mol) in DMF (5.0 mL) was degassed using house vacuum, and purged with argon (3 cycles).

Then added diisopropylethylamine, (0.5 mL) followed by the addition of PdCl2(PPh3)2 (0.36 g). The reaction mixture was heated at 65 °C for 1.5 h under argon atmosphere. The solvents were distilled in vacuo, and the residue was purified by silica gel flash chromatography using EtOAc/hexane (2:3 v/v) to afford 0.65 g (70%) of the title compound as a brown colored amorphous solid: ^{1}H- NMR (CD3OD/400 MHz) δ 7.59 (m, 2H), 7.45 - 7.3 (m, 4H), 7.05 - 6.85 (m, 3H), 6.44 (s, 1H), 5.41 (s, 2H), and 2.31 (s, 3H); ^{19}F-NMR (CD3OD/400 MHz) δ -116.33 (m); ESHRMS m/z 396.0373 (M+H C21H16NOBrF 396.0399).

Step 5: Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one

To a solution of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one (0.55 g, 0.0014 mol) in EtOAc (10.0 mL) and EtOH (10.0 mL) was added PtO2 (0.05g) and stirred in an atmosphere of hydrogen gas at 15 psi for 30 min. The catalyst was removed by filtration, the filtrate was concentrated and the residue was purified by silica gel flash chromatography using 25% EtOAc in hexane as the eluent. The appropriate fractions were combined (visualized under UV) and concentrated to dryness. ^{1}H- NMR (CD3OD/400 MHz) δ 7.35 (m, 1H), 7.31 - 7.16 (m, 5H), 6.99(m, 1H), 6.91 (m, 1H), 6.81 (m, 1H), 6.20 (s, 1H), 5.41 (s, 2H), 2.94 (m, 4H), and 2.24 (s, 3H); ^{19}F-NMR (CD3OD/400 MHz) δ -115.01 (m); ESHRMS m/z 400.0695 (M+H C21H20NOBrF 400.0712).

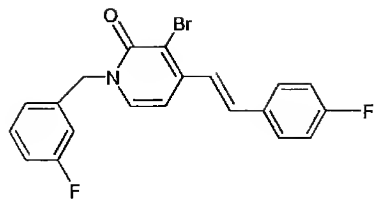
Example 361



3-bromo-1-(3-fluorobenzyl)-4-(1-phenylethoxy)pyridin-2(1H)-one

A mixture of 3-bromo-1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (0.2 g, 0.72mmol), potassium carbonate (0.1 g, 0.72 mmol) and (1-bromoethyl)benzene (0.19 g, 1 mmol) in DMF (3.0 mL) was stirred at room temperature for 16 h. DMF was distilled in vacuo, and the residue was purified by flash chromatography (EtOAc in hexane (1:3 v/v) to give pale yellow syrup. This material was further purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min), at flow rate of 100 mL/min. The appropriate fractions were combined, concentrated to a small volume (20 mL), added EtOAc (25 mL) and washed successively with satd. sod. bicarbonate, water, and dried (Na_2SO_4). EtOAc was removed under reduced pressure and residue was dried in vacuo to afford the title compound (0.15 g, 52%) as an amorphous substance: ^1H NMR (CD_3OD/ 400 MHz) δ 7.56 (d, 1H, J = 7.6 Hz), 7.4 - 7.2 (m, 5H), 7.0 (m, 3H), 6.28 (d, 1H, J = 7.6 Hz), 5.65 (m, 1H), 5.19 (d x d, 2H, J = 14.8 Hz), and 1.64 (d, 3H, J = 6.4 Hz), ES-HRMS m/z 402.0492 (M+H $C_{20}H_{18}NO_2Br$, requires 402.0499).

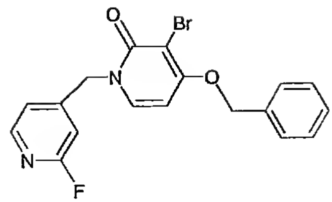
Example 362



3-bromo-1-(3-fluorobenzyl)-4-[(E)-2-(4-fluorophenyl)ethenyl]pyridin-2(1H)-one

A mixture of 3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1.0 g, 0.0023 mol)', and 4-fluorostyrene (0.33 mL,, 0.0028 mol) in degassed DMF (10 0 ml) containing diisopropyl ethyl amine (0.37 g, 0.0029 mol) was treated with $PdCl_2(PPh_3)_2$ (0.32 g, 0.46 mmol) and heated at 65 °C under argon atmosphere for 16 h. DMF was distilled in vacuo, and the residue was purified by flash chromatography (EtOAc/ hexane 1:4 v/v) to afford a yellow substance which was further purified by by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min), at flow rate of 100 mL/min. The appropriate fractions were combined, concentrated to a small volume (20 mL), added EtOAc (25 mL) and washed successively with satd. sod. bicarbonate, water, and dried (Na_2SO_4). EtOAc was removed under reduced pressure and residue was dried in vacuo to afford the title compound (0.06 g, 6%) as yellow powder: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.68 (m, 3H), 7.39 (m, 3H), 7.2 - 7.0 (m, 5H), 6.82 (d, 1H, J = 7.2 Hz), and 5.22 (s, 2H); ^{19}F NMR(CD_3OD/ 400 MHz) δ -113.9(m) and -115 (m); ES-HRMS m/z 402.0305 (M+H $C_{20}H_{15}NOF_2Br$, requires 402.0300).

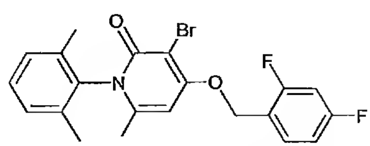
Example 363



4-(Benzyloxy)-3-bromo-1-[(6-fluoropyridin-3-yl)methyl]pyridin-2(1H)-one

A mixture of 4-(benzyloxy)-3-bromopyridin-2(1H)-one (0.2 g, 0.00076 mol), 5-bromomethyl-2-fluoropyridine (0.25 g, 0.0013 mol) and pot. Carbonate (0.15 g, 0.0011 mol) in DMF (3.0 ml) was stirred at room temperature for 16 h under argon atmosphere. DMF was distilled in vacuo and the residue was partitioned between water (15 ml) and EtOAc (25 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.22 (m, 1H, 2.4 Hz), 7.92(m, 1H), 7.82 (d, 1H, J = 7.6 Hz), 7.44 - 7.31 (m 5H), 7.03(m, 1H) 6.49 (d, 1H, J = 7.6 Hz),5.29 (s, 2H), and 5.20 (s, 2H); ^{19}F NMR(CD_3OD/ 400 MHz) δ -72.30 (d, J = 6.0 Hz) and -115 (m); ES-HRMS m/z 389.0295 (M+H $C_{18}H_{15}N_2O_2FBr$, requires 389.0309).

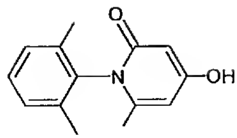
Example 364



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1H)-one

STEP1

Preparation of

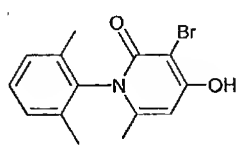


1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

A mixture of 4-hydroxy-6-methyl-2-pyrone (2.5 g, 0.02 mol), 2,6 dimethylaniline (2.4 g, 0.02 mol), and p-toluenesulfonic acid (0.2 g) as heated at 140 °C for 3 h under nitrogen atmosphere. The reaction mixture was cooled, triturated with acetonitrile , cooled and filtered the solids.
^{1}H NMR (CD_3OD/ 400 MHz) δ 7.22 (m, 3H), 6.12 (d, 1H, J = 1.6 Hz), 5.83 (d, 1H, J = 1.8 Hz), 2.00 (s, 6H), and 1.82 (s, 3H); ESMS m/z 229 (M+H).

Step 2

Preparation of



3-Bromo-1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

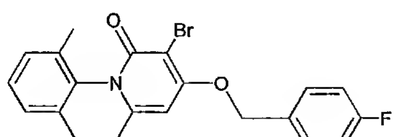
A mixture of 1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.4 g, 0.00175 mol), and NBS (0.35 g, 0.0019 mol) in dichloromethane (10.0 ml) was stirred at room temperature under nitrogen atmosphere. After 1 h, the

solids were filtered, washed with dicholoromethane to give 0.42 g (78%) of the title compd as a pale yellow powder: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.22 (m, 3H), 6.21 (s, 1H), 1.99 (s, 6H), and 1.82 (s, 3H); ESMS m/z 308/310 (M+H).

Step 3

A mixture of 3-Bromo-1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.15 g, 0.00049 mol), 2,4 difluorobenzyl bromide (0.12 g, 0.00058 mol) and potassium carbonate (0.075 g, 0.00054 mol) in DMF 3.00 mL) was stirred at room temperature uder argon atmosphere for 2h. It was then heated at 60 °C for 30 min and concentrated in vacuo. The residue was purified by flash chromatography. ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.62 (m, 1H), 7.28 (m,3H), 7.04 (m, 2H), 6.68 (s, 1H), 5.35 (m, 1H), 1.98 (s, 6H), and 1.92 (s, 3H); ES-HRMS m/z 434.0574 (M+H $C_{21}H_{19}NO_2F_2Br$, requires 434.0562).

Example 365

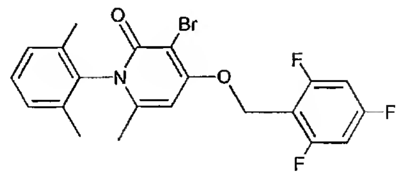


3-Bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 364. ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.58 (m, 2H), 7.23 (m, 3H), 7.15 (m, 2H), 6.62 (s, 1H), 5.32

(s, 2H), 1.98 (m, 6H), and 1.91 (s, 3H); ES-HRMS m/z 416.0670. (M+H $C_{21}H_{20}NO_2FBr$, requires 416.0656).

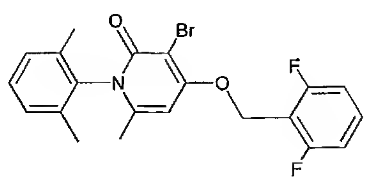
Example 366



3-Bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for EXAMPLE 364. ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.19 (m, 3H), 6.95 (m, 2H), 6.69 (s, 1H), 5.29 (s, 2H), 1.95 (s, 6H), and1.90 (s, 3H); ES-HRMS m/z 452.0471. (M+H $C_{21}H_{18}NO_2F_3Br$, requires 452.0468).

Example 367

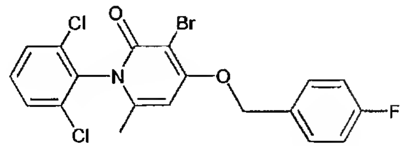


3-Bromo-4-[(2,6-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1H)-one.

The title compound was prepared by a procedure similar to the one described for EXAMPLE 364. ^{1}H NMR (CD_3OD/ 400 MHz) δ

7.46 (m, 1H), 7.24 (m, 3H), 7.08 (m, 2H), 6.74 (s, 1H), 5.38 (s, 2H), 1.99 (s, 6H), and 1.94 (s, 3H); ES-HRMS m/z 434.0589 (M+H $C_{21}H_{19}NO_2F_2Br$, requires 434.0562).

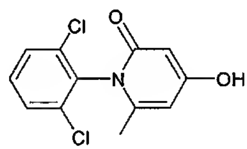
Example 368



3-Bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1

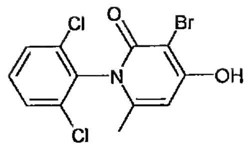
Preparation of 1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



This compound was prepared by a procedure similar to the one described in step 1 for EXAMPLE 364. Yield: 28%, ^{1}H NMR (CD3OD) δ 7.6 (m, 2H), 7.48 (m, 1H), 6.10 (dd, 1H), 5.78 (d, 1H, J = 2.4 Hz), 1.91 (s, 3H); (ES-MS m/z = 270 (MH$^+$);

Step 2

Preparation of 3-bromo-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

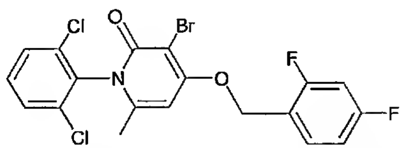


This compound was prepared by a procedure similar to the one described in step 2 for EXAMPLE 364. Yield: 78%, ^{1}H NMR (400 MHz) CD_3OD δ 7.61 (m, 2H), 7.49 (m, 1H), 6.2 (s, 1H), and 1.91 (s, 3H); ES-MS, m/z = 348 (MH^+).

Step 3

This compound was prepared by a procedure similar to the one described in step 3 for EXAMPLE 364. Yield: 44%, ^{1}H NMR (CD_3OD) δ 7.62 (d, 2H, J = 8.0 Hz), 7.51 (m, 3H), 7.15 (m, 2H), 6.64 (s, 1H), 5.33 (s, 2H), and 2.0 (s, 3H); ^{19}F NMR (CD_3OD) δ -166.21 (m); ES-HRMS m/z 455.9541 (M+H $C_{19}H_{14}NO_2Cl_2BrF$, requires 455.9564).

Example 369



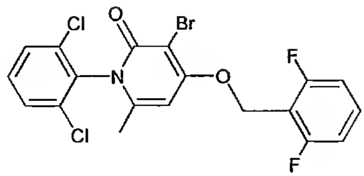
3-Bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

This compound was prepared by a procedure similar to the one described for EXAMPLE 368.

Yield: 64%, ^{1}H NMR (CD_3OD/400 MHz δ 7.62 (m, 3H), 7.48 (m, 1H), 7.05 (m, 2H), 6.70 (s, 1H), 5.36 (s, 2H), and 2.02 (s, 3H), ^{19}F NMR (CD_3OD) δ -111.43 (m) and

-115.89 (m); ES-HRMS m/z 473.9450 (M+H $C_{19}H_{13}NO_2Cl_2BrF_2$, requires 473.9469).

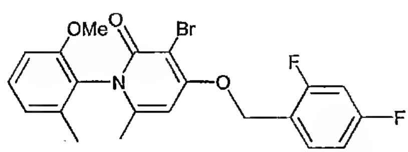
Example 370



3-Bromo-1-(2,6-dichlorophenyl)-4-[(2,6-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

This compound was prepared by a procedure similar to the one described for EXAMPLE 368. Yield: 78%, ^{1}H NMR (CD_3OD/400 MHz) δ 7.62 (d, 2H, J = 8.0 Hz), 7.52 (m, 2H), 7.1 (m, 2H), 6.77 (s, 1H), and 2.04 (s, 3H); ^{19}F NMR (CD_3OD) δ -117.04 (m); ES-HRMS m/z 473.9468 (M+H $C_{19}H_{13}NO_2Cl_2BrF_2$, requires 473.9469).

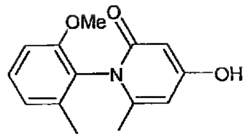
Example 371



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one

Step 1

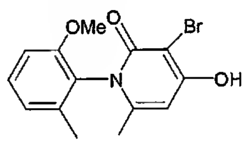
Preparation of 4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one



This compound was prepared by a procedure similar to the one described in step 1 for EXAMPLE 368. Yield: 21%, ^{1}H NMR (CD_3OD/400 MHz) δ 7.31 (m, 1H), 6.94 (m, 2H), 6.05 (d, 1H, J = 2.4 Hz), 5.78 (d, 1H, J = 2.4 Hz), 3.76 (s, 3H), 2.00 (s, 3H), and 1.83 (s, 3H); ES-HRMS m/z 246.1092 (M+H $C_{14}H_{16}NO_3$, requires 246.1123).

Step 2

Preparation of 3-bromo-4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one



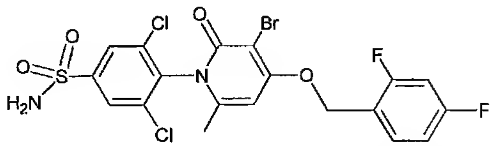
This compound was prepared by a procedure similar to the one described in step 2 for EXAMPLE 368. Yield: 58%, ^{1}H NMR (CD_3OD/400 MHz) δ 7.34 (m, 1H), 6.96 m (2H), 6.15 (s, 1H), 3.76 (s, 3H), 1.99 (s, 3H), and 1.83 (s, 3H); ESMS m/z 324 (M+H).

Step 3

This compound was prepared by a procedure similar to the one described for EXAMPLE 368. Yield: 60%, ^{1}H NMR (CD_3OD/400MHz) δ 7.63 (m, 1H), 7.36 (m, 1H), 7.01 (m, 4H), 6.61 (s, 1H), 5.33 (s, 2H), 3.76 (s, 3H), 1.99(s, 3H), and 1.95 (s, 3H); ^{19}F NMR

(CD_3OD/400 MHz) δ -111.64 (m), and -116.03 (m); ES-HRMS m/z 450.0532 (M+H $C_{21}H_{19}NO_3Cl_2BrF_2$, requires 450.0511).

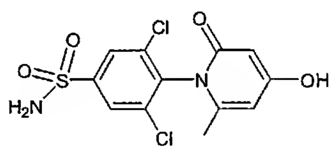
Example 372



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-dichlorobenzenesulfonamide

Step 1

Preparation of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide



A mixture of 4-hydroxy-6-methylpyrone ((1.2 g, 0.0095 mol), and 2,6-dichlorosulphanilamide (2.4 g, 0.0099 mol) was heated at 170 °C under argon for 20 min. The resulting dark colored melt was cooled and the crude material was first purified by flash chromatography (EtOAc) to give partially purified material which contained the desired product. This was further purified by reverse-phase HPLC using 10 - 90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 349)were combined and freeze

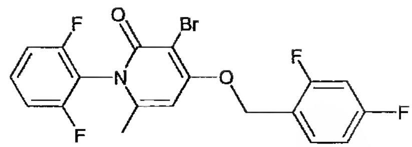
dried to afford 0.19 g of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide as pale yellow solid: ^{1}H NMR (CD_3OD/400 MHz) δ 8.06 (s, 2H), 6.13 (d, 1H, J = 1.6 Hz), 5.78 (d, 1H, J = 1.6 Hz), and 1.94 (s, 3H)); ES-HRMS m/z 348.9819 (M+H $C_{12}H_{11}N_2O_4SCl_2$ requires 348.9811).

Step 2

A mixture of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide (0.18 g, 0.0005 mol), N-bromosuccinimide (0.1 g, 0.00056 mol)in acetici acid (2.0 mL) was stirred at room temperature under argon atmosphere for 1 h. Acetic acid was removed in vacuo, the residue was dissolved in DMF (2.0 mL), and added 2,4 difluorobenzyl bromide (0.128 g, 0.0006 mol), potassium carbonate (0.1 g, 0.0007 mol). The resulting mixture was stirred at room temperature for 1 h. The solvents were distilled in vacuo, and the residue was purified by flash chromatography (EtOAc/ hexane 1: 3 v/v) to give 0.14 g of partially purified product. This was further purified by reverse-phase HPLC using 10 - 90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 553) were combined and freeze dried to afford 0.045 g of pale yellow powder. This was partitioned between EtOAc (25 ml) and 5% sod. bicarbonate. The organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. This material was dried invacuo to afford the title compound (0.033 g) as a white amorphous substance:

^{1}H NMR ($CDCl_3$/400 MHz) δ 7.99 (s, 2H), 7.59 (m, 1H), 6.98 (m, 1H), 6.85 (m, 1H), 6.23 (s, 1H), 5.69 (s, 2H), 5.28 (s, 2H), 1.97 (s, 3H), and 1,76 (br, 2H); ES-HRMS m/z 552.7214 (M+H $C_{19}H_{14}BrCl_2N_2O_4S$ requires 552.9197).

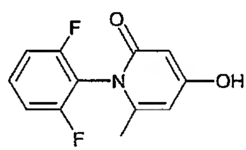
Example 373



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1

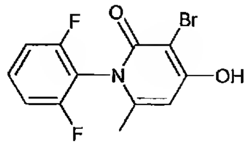
Preparation of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



A mixture of 4-hydroxy-6-methyl-2-pyrone (10.0 g, 0.079 mol) and 2,6 difluoroaniline (9.5 g, 0.073 mol) was heated at 170 °C under argon atmosphere for 20 min. The water formed was removed using a Dean-stark apparatus. The melt was cooled, the dark solid was tritutrated with EtOAc., and filtered. This material was washed thoroughly with EtOAc to afford the desired product 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one 6.5 g (35%) as a light brown solid: ^{1}H NMR (CD_3OD/400 MHz) δ 7.56 (m, 1H), 7.19 (m, 2H), 6.09 (m, 1H), 5.77 (d, 1H, J = 2.4 Hz), and 1.99 (s, 3H); ES-HRMS m/z 238.0679 (M+H $C_{12}H_{10}NO_2F_2$ requires 238.0674).

Step 2

Preparation of 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



The title compound was prepared by a procedure described in step2 for EXAMPLE 364.

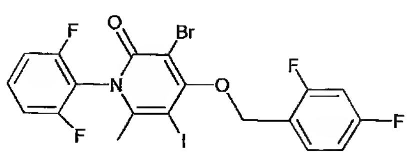
Yield: 79%, ^{1}H NMR (CD_3OD/400 MHz) δ 7.58 (m, 1H), 7.21 (m, 2H), 6.19 (d, 1H, J = 0.8 Hz), 1.99 (s, 3H); ES-HRMS m/z 315.9811 (M+H $C_{12}H_9NO_2F_2Br$ requires 315.9779).

Step 3

This compound was prepared by a procedure described in step 3 for EXAMPLE 364.

Yield : 63%, ^{1}H NMR (CD_3OD) δ 7.58 (m, 2H), 7.23 (m, 2H), 7,06 (m, 2H), 6.68 (s, 1H), 5.36 (s, 2H), and 2.10 (s, 3H); ^{19}F NMR (CD_3OD) δ − 111.50 (m), -115.96 (m), and -121.93 (m); ES-HRMS m/z 442.0061 (M+H $C_{19}H_{13}NO_2F_4Br$ requires 442.0060).

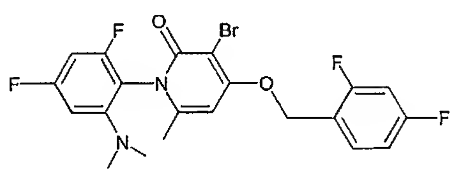
Example 374



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

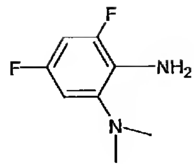
A solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (0.3 g, 0.00068 mol) and N-iodosuccinimide (0.22 g, 0.00098 mol) in dichloroethane , containing dichloroacetic acid (0.1 mL) was heated to reflux for 6 h under argon atmosphere. After the removal of the solvents under reduced pressure, the residue was partitioned between, dichloromethane (20 mL) and 5% sod. sulphite (10 mL). The organic phase was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc in hexane) to afford the title compound (0.125 g, 32 %) as a pale yellow powder: ^1H NMR ($CDCl_3$/400 MHz) δ 7.68 (m, 1H), 7.46 (m, 1H), 7.11 (m, 2H), 6.95 (m, 1H), 6.85 (m, 1H), 5.23 (s, 2H), and 2.38 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −109.15 (m), -112.95 (m), -118.50 (m); ES-HRMS m/z 567.9014 (M+H $C_{19}H_{12}NO_2F_4BrI$ requires 567.9027).

Example 375



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1H)-one

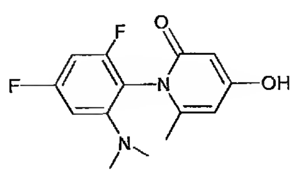
Step 1



3,5-difluoro-N~1~,N~1~-dimethylbenzene-1,2-diamine

To a solution of 2,4,6-trifluoronitrobenzene (2.58 g, 0.0145 mol) in THF (20.0 ml) was added a solution of N,N-dimethylamine in THF (8.5 mL of 2M soln) and stirred for 45 min at 0 °C. It was then stirred at room temperature for 30 min and concentrated to dryness. The resulting material was dissolved in EtOH (25 mL), added Pd/C (10%, 0.6 g) and hydrogenated at 50 psi for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under reducued pressure. Te residue was partitioned between sod. bicarbonate (10%, 25 mL) and EtOAc (30 mL). The organic phase was washed with water, dried (Na_2SO_4), and concentrated to dryness to afford the title compound (1.3 g, 50%) as a dark colored solid: ^1H NMR ($CDCl_3$/400 MHz) δ 6.52 (m, 2H), 3.64 (br, 2H), and 2.65 (s, 6H); ES-HRMS m/z 172.0772 (M+ $C_8H_{10}N_2F_2$ requires 172.0810).

Step 2

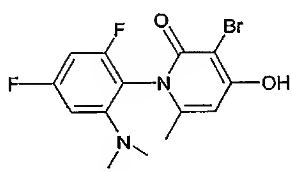


1-[2-(dimethylamino)-4,6-difluorophenyl]-4-hydroxy-6-methylpyridin-2(1H)-one

An intimate mixture of 4-hydroxy-6-methyl-2-pyrone (1.3 g, 0.0103 mol), and 3,5- difluoro-N,N-dimethylbenzene-1,2-diamine (1.4 g, 0.008 mol) was heated at 160 °C under argon for 15 min. The dark colored reaction mixture was cooled, triturated with EtOAc (15 ml), and filtered. The solids were washed with warm EtOAc, followed by hexane and dried to give the title compound as a light blue solid (0.4 g, 14 %). Analalytically pure sample was prepared by reverse-phase HPLC purification using 10 -90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions were combined and freeze-dried to give the title compound: ^1H NMR (CD_3OD/400 MHz) δ 6.61 (m, 2H), 6.08 (d, 1H, J = 2.0 Hz), 6.78 (d, 1H, J = 2.0 Hz), 2.69 (s, 6H), and 1.94 (s, 3H); ES-HRMS m/z 281.1084 (M+H $C_{14}H_{15}N_2O_2F_2$ requires 281.1096).

Step 2

Preparation of



3-bromo-1-[2-(dimethylamino)-4,6-difluorophenyl]-4-hydroxy-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure described in step2 for EXAMPLE 364. Yield:71%, ^1H NMR (CD_3OD/400 MHz) δ 6.62 (m, 2H), 6.17 (s, 1H), 2.67 (s, 6H), and 1.94 (s, 3H); ES-HRMS m/z 359.0188 (M+H $C_{14}H_{14}N_2O_2F_2Br$ requires 359.0201).

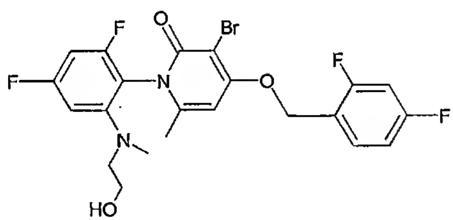
Step 3

This compound was prepared by a procedure described in step 3 for EXAMPLE 364.

Yield : 34%, ^{1}H NMR ($CDCl_3$/400 MHz) δ 7.62 (m, 1H), 6.98 (m, 1H), 6.85 (m, 1H), 6.46 (m, 2H), 6.11 (s, 1H), 5.24 (s, 2H), 2.66 (s, 6H), and 1.98 (s, 3H); ^{19}F NMR ($CDCl_3$/400 MHz) δ -108.06 (m), -109.60 (m), - 115.02 (m), and -116.01 (m); ES-HRMS m/z 485.0451 (M+H $C_{21}H_{18}N_2O_2F_4Br$ requires 485.0482).

The title compound was prepared by stirring a suspension of thet product of step 3, above, (0.14 g) with 4N HCl in dioxane (0.7 mL) at room temperature for 30 min. The mixture was concentrated to dryness. ^{1}H NMR (CD_3OD/400 MHz) δ 7.62 (m, 1H), 7.02 (m, 2H), 6.65 (m, 3H), 5.34 (s, 2H), 2.66 (s, 6H), and 2.05 (s, 3H); ESMS m/z = 485.

Example 376

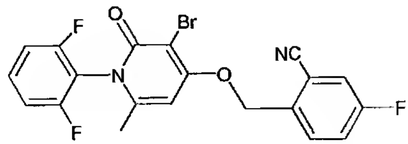


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1H)-one

The title compound was prepared by a similar procedure described for EXAMPLE 375, replacing N,N-dimethyl group by N-Methyl-aminoethanol. ^{1}H NMR ($CDCl_3$/400 MHz) δ 7.59 (m, 1H), 6.98 (m, 1H), 6.85 (m, 1H), 6.61 (m, 1H), 6.52 (m, 1H), 6.17 (m, 1H), 5.25 (s, 2H), 3.63 (m, 1H), 3.53 (m, 1H), 3.26 (m, 1H),

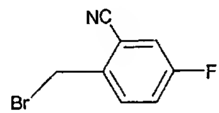
3.0 (m, 1H), 2.66 (s, 6H), and 2.09 (s, 3H); ES-HRMS m/z 515.0512 (M+H $C_{22}H_{20}N_2O_3F_4Br$ requires 515.0588).

Example 377



2-({[3-Bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile

Step 1



2-(Bromomethyl)-5-fluorobenzonitrile

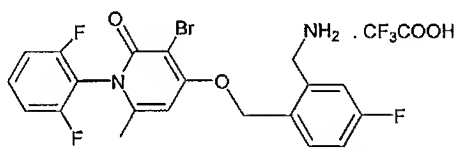
A mixture of 5-fluoro-2-methylbenzonitrile (2.0 g, 0.015 mol), NBS (3.2 g, 0.018 mol) and benzoylperoxide (0.25 g) in carbontetrachloride (25.0 ml) was heated to reflux for 6 h, under argon atmosphere. The reaction mixture was cooled and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (5% EtOAc in hexane) to afford 2-(Bromomethyl)-5-fluorobenzonitrile (1.9 g, 60%) as a colorless liquid: ^{1}H NMR ($CDCl_3$/400 MHz) δ 7.59 (m) 7.58 (m, 1H), 7.38 (m, 1H), and 7.25 (m, 1H).

Step 2

A mixture of 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

1.0 g, 0.0032 mol), potassium carbonate (0.65 g, 0.0047 mol) and 2-(Bromomethyl) 5-fluorobenzonitrile (0.95 g, 0.0045 mol) in dimethylacetamide (15.0 ml) was stirred at room temperature under argon atmosphere. After 1h, dimethylacetamide was distilled in vacuo and the residue was partitioned between dichloromethane (50 ml) and 55 citric acid (15 mL). The organic phase was washed with water, dried (Na_2SO_4), and concentrated to dryness. The resulting material was triturated with EtOAc, filtered, washed with EtOAc and dried to afford the title compound (0.86 g, 60%) as a white powder: ^{1}H NMR (DMSO-d_6/400 MHz) δ 7.95 (m, 1H), 7.81 (m, 1H), 7.68 (m, 2H), 7.37 (m, 2H), 6.79 (s, 1H), 5.45 (s, 2H), and 2.03 (s, 3H); ^{19}F- NMR (DMSO-d_6) δ -111.31 (m), -120.34 (m); ES-HRMS m/z 449.0094 (M+H $C_{20}H_{13}N_2O_2F_3Br$ requires 449.0107).

Example 378

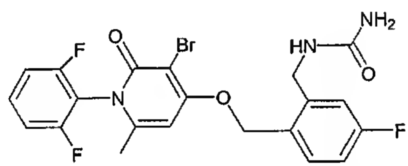


4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a cold suspension of 2-({[3-Bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile (0.3 g, 0.00066 mol) in THF (3.0 mL), was added BH_3.THF (1.0 mL). After stirring at room temperature for 15 min, the reaction mixture was heated to reflux for 30 min under argon atmosphere. The resulting clear solution cooled,

added MeOH (2.0 mL), concentrated under reduced pressure, and the residue was purified by reverse-phase HPLC purification using 10 -90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 453 M+H) were combined and freeze-dried to give the title compound (0.16 g, 43%) as its trifluoroacetate salt: ^1H NMR (DMSO-d_6/400 MHz) δ 8.19 (br, 3H), 7.65 (m, 2H), 7.37 (m, 4H), 6.78 (s, 1H), 5.42 (s, 2H), 4.21 (br, 2H), and 2.04 (s, 3H); ^{19}F NMR (DMSO-d_6/400 MHz) δ -112.96 (m), and -120.41 (m); ES-HRMS m/z 453.0387 (M+H $C_{20}H_{17}N_2O_3F_3Br$ requires 453.0420).

Example 379

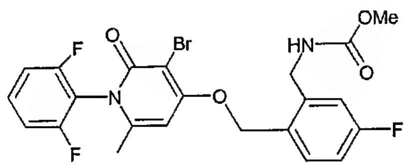


N-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]urea

To a suspension of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.13g, 0.00023 mol) in THF (3.0 mL), was added triethyl amine (0.07 mL, 0.0005 mol) followed by the addition of trimethylsilylisocyanate (0.066 mL). The reaction mixture was stirred at room temperature for 1 h, and the desired product was isolated by reverse-phase HPLC purification using 10 -90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 496 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod. bicarbonate (20 mL) and dichloromethane (20

mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness under reduced pressure, to afford the title compound as a white amorphous powder (0.065 g): ^1H NMR (DMSO-d_6/400 MHz) δ 7.62 (m, 1H), 7.52 (m, 1H), 7.35 (m, 2H), 7.09 (m, 2H), 6.77 (s, 1H), 6.51 (t, 1H), 5.61 (s, 2H), 5.38 (s. 2H), 4.28 (d, 2H, J = 6.0 Hz), and 2.02 (s, 3H); ^{19}F NMR (DMSO-d_6/400 MHz) δ -114.044 (m), and -120.31 (m); ES-HRMS m/z 496.0460 (M+H $C_{21}H_{18}N_3O_3F_3Br$ requires 496.0478).

Example 380

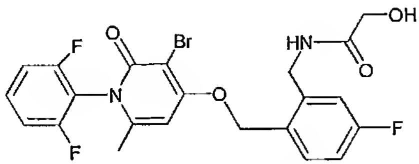


Methyl 2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.12g, 0.00021 mol) in dimethylacetamide (2.0 mL) at 0 °C, was added triethylamine (0.06 mL, 0.00043 mol) followed by the addition of methylchloroformate (0.05 mL). The reaction mixture was stirred at room temperature for 30 min under argon atmosphere. Dimethylacetamide was distilled in vacuo and the residue was partitioned between dichloromethane (10 mL) and 5% citric acid (10 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by flash chromatography (60%EtOAc in hexane) to afford the title compound (0.09 g, 75%) as a white amorphous powder: ^1H NMR (DMSO-d_6/400 MHz) δ 7.68 (m, 1H), 7.62 (m, 1H), 7.59 (m, 1H),

7.38 (m, 2H), 7.115 (m, 2H), 6.78 (s, 1H), 5.38 (s, 2H), 4.31 (d, 2H, J = 6.0 Hz), 3.53 (s, 3H), and 2.03 (s, 3H); ^{19}F NMR (DMSO-d_6/400 MHz) δ -113.77 (m), and -120.33 (m); ES-HRMS m/z 511.0508 (M+H $C_{22}H_{19}N_2O_4F_3Br$ requires 511.0475).

Example 381

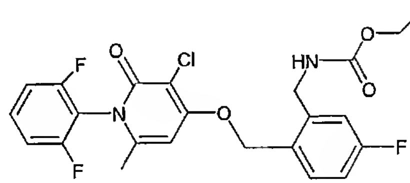


N-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]-2-hydroxyacetamide

To a suspension of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.12g, 0.00021 mol) in THF (2.0 mL) at 5 °C, was added triethyl amine (0.036 g, 0.00035 mol) followed by the addition of acetoxyacetyl chloride (0.05 mL). The mixture was stirred at room temperature for 30 min, diluted with cold water (10 mL), and extracted the products with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness. The residue was dissolved in ethanol (0.5 mL), added 1N NaoH (0.5 mL)and stirred at room temperature for 1 h. The resulting solution was diluted with water (15 mL), and extracted with dichloromethane (2 x 10 mL). The combined dichloromethane extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness. The residue was purified by flash chromatography (1% MeOH in EtOAc) to afford the title compound

(0.032 g, 30 %) as a white amorphous powder: ^{1}H NMR ($CDCl_3$/400 Hz) δ 7.45 (m, 2H), 7.18 (m, 1H), 7.05 (m, 3H), 6.23 (s, 1H), 5.24 (s, 2H), 4.56 (d, 2H, J = 6.4 Hz), 4.08 (d, 2H, J = 5.2 Hz), 2.79 (t, 1H), and 2.08 (s, 3H;) ^{19}F NMR ($CDCl_3$/400 MHz) δ − 111.88 (m), and -118.62 (m); ES-HRMS m/z 511.0482 (M+H $C_{22}H_{19}N_2O_4F_3Br$ requires 511.0475).

Example 382

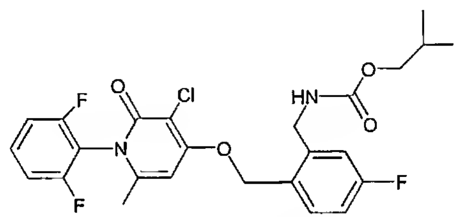


Ethyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.3g, 0.00057 mol) in dimethylacetamide (3.0 mL) was added N-methymorpholine (0.064 g, 0.00064 mol), followed by addition of ethylchloroformate (0.06 mL) and stirred at − 10 °C, for 30 min. The solvents were distilled in vacuo and the residue was purified by reverse-phase HPLC purification using 10 -90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 481 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod. bicarbonate (20 mL) and dichloromethane (20 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness under reduced pressure, to afford the title compound as a white amorphous powder (0.15 g, 55%): ^{1}H NMR (CD_3OD/400MHz) δ 7.61 (m, 1H), 7.52

(m, 1H), 7.26 (~t, 2H, J = 8.4 Hz), 7.12 (dd, 1H), 7.05 (3d, 1H, J = 2.4 Hz), 6.74 (s, 1H), 5.40 (s, 2H), 4.42 (s, 2H), 4.05 (q, 2H, J = 7.2 Hz), 2.12 (s, 3H), and 1.21 (t, 3H, J = 7.2 Hz); ES-HRMS m/z 481.1118 (M+H $C_{23}H_{21}N_2O_4F_3Cl$ requires 481.1136).

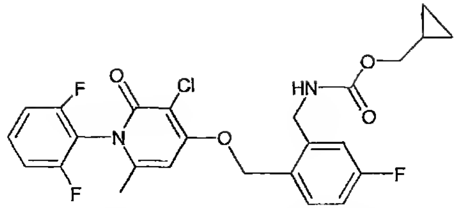
Example 383



Isobutyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared by a procedure similar to the one described for EXAMPLE 382. Yield 57 %; ^{1}H NMR (CD_3OD/400 MHz) δ 7.61 (m, 1H), 7.51 (m, 1H), 7.24 (~t, 2H, J = 8.0 Hz), 7.18 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.40 (s, 2H), 4.21 (s, 2H), 3.79 (d. 2H, J = 6.8 Hz), 2.12 (s, 3H), 1.85 (m, 1H), and 0.91 (d, 6H, J = 6.4 Hz); ES-HRMS m/z 509.1422 (M+H $C_{25}H_{25}N_2O_4F_3Cl$ requires 509.1449)

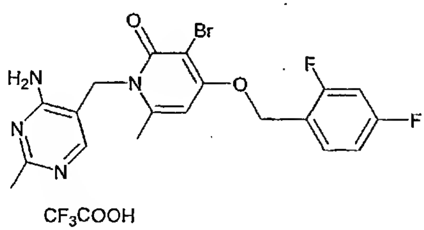
Example 384



Cyclopropylmethyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

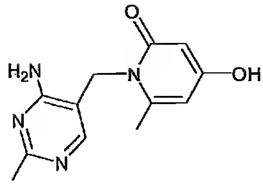
The title compound was prepared by a procedure similar to the one described for EXAMPLE 382. Yield 46%; ^{1}H NMR (CD_3OD/400 Hz) δ 7.61 (m, 1H), 7.55 (m, 1H), 7.24 (~ t, 2H, J = 7.6 Hz), 7.18 (m, 1H), 7.05 (m, 1H), 6.73 (s, 1H), 5.40 (s, 2H), 4.42 (s, 2H), 3.83 (d, 2H, J = 7.2 Hz), 2.12 (s, 3H), 1.1 (br, 1H), 0.58 (~d, 2H), and 0.22 (~ d, 2H); ES-HRMS m/z 507.1316 (M+H $C_{25}H_{23}N_2O_4F_3Cl$ requires 507.1293).

Example 385



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

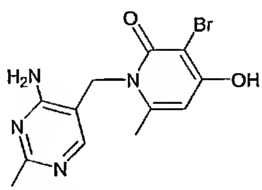
Step 1



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-hydroxy-6-methylpyridin-2(1H)-one

A mixture of 4-hydroxy-6-methyl-2-pyrone (0.9 g, 0.007 mol) and 4-amino-5-aminomethyl-2-methylpyrimidine (1.0 g, 0.007 mol) in water (10.0 ml) was heated at 100 °C for 1 h under argon atmosphere. The reaction mixture was cooled, and filtered the yellow precipitate. It was washed successively with cold water, ethanol, and dried in vacuo to afford the title compound (1.01 g, 51%) as a pale yellow powder: ^{1}H NMR (DMSO-d_6/400 MHz) δ 7.62 (s, 1H), 7.04 (s, 1H), 5.83 (d, 1H, J = 2.0 Hz), 5.58 (d, 1H, J = 2.0 Hz), 4.92 (s, 2H), 2.24 (s, 3H), and 2.22 (s, 3H); ES-HRMS m/z 325.0304 (M+H $C_{12}H_{14}N_4O_2Br$ requires 325.0295).

Step 2



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one

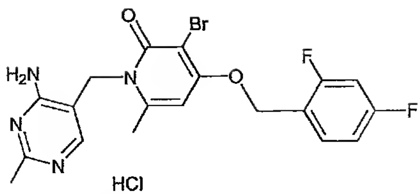
A mixture of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-hydroxy-6-methylpyridin-2(1H)-one (0.5 g, 0.002 mol), and NBS (0.4 g, 0.002 mol) in glacial acetic acid (5.0 ml) was stirred

at room temperature for 1 h under argon atmosphere. Acetic acid was removed in vacuo, residue was triturated with EtOAc containing 10 % EtOH, and filtered. The pale yellow precipitate was washed with EtOAc containing 10% EtOH and dried in vacuo to afford the title compound (0.47 g, 725) as a pale yellow powder: ^1H NMR (CD_3OD/400 MHz) δ 7.62 (s, 1H), 6.09 (s, 1H), 5.15 (s, 2H), 2.42 (s, 3H), and 2.33 (s, 3H); ES-HRMS m/z 247.1160 (M+H $C_{12}H_{15}N_4O_2$ requires 247.1190).

Step 3

To suspension of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one (1.0 g, 0.0031 mol) and potassium carbonate (0.0 g, 0.004 mol) in dimethylacetamide (10.0 mL) was added 2,4 difluorobenzyl bromide (0.62 mL, 0.0048 mol) and stirred at room temperature for 2 hours. Dimethylacetamide was distilled in vacuo and the residue was purified by reverse-phase HPLC using 10 - 90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 566)were combined and freeze dried to afford 0.65 g (37 %) of the title compound as its trifluoroacetate salt: ^1H NMR (CD_3OD/400 MHz) δ 7.65 (s, 1H), 7.58 (m, 1H), 7.05 (m, 2H), 6.61 (s, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 2.51 (s. 3H), and 2.46 (s, 3H); ^1H NMR (CD_3OD/400 MHz) δ −111.39 (m), and −115.98 (m); ES-HRMS m/z 451.0590 (M+H $C_{19}H_{18}N_4O_2BrF_2$ requires 451.0576).

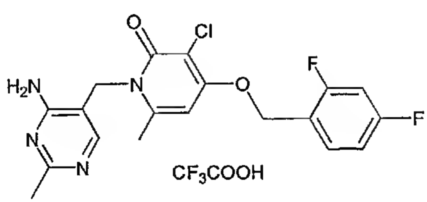
Example 386



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

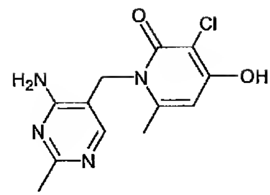
Ion exchange (25g) BioRad AG 2X8 resin (200-400 mesh chloride form) was washed with 1M HCl (150 mL), and equilibrated for 2.5 h. This resin was loaded onto a column, and added a solution of Example 385 (3.3 g, 5.8 mmol) in water/CH_3CN (1:1). The column was eluted slowly over 1 h, fractions were collected, and freeze dried to afford the desired HCl salt (2.2 g, 72%) as a white solid: ^{1}H-NMR (CD_3OD, 400Hz) δ 7.60 (m, 2H), 7.21 (m, 2H), 6.62 (s, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 2.52 (s, 3H), 2.47 (s,3H); ES-HRMS m/z 451.0544/453.0577 (M+H $C_{19}H_{17}N_4O_2F_2Br$ requires 451.0581/453.0563).

Example 387



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

Step 1. Preparation of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-hydroxy-6-methylpyridin-2(1H)-one

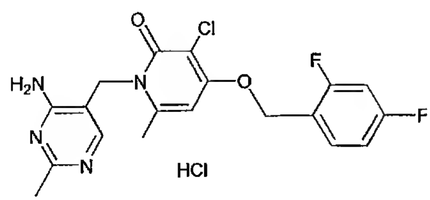


^{1}H NMR (CD_3OD, 400Hz) δ 7.62 (m, 1H), 6.11 (s, 1H), 5.13 (s, 2H), 2.66 (s, 3H), 2.42 (s,3H); ES-HRMS m/z 281.0793 (M+H $C_{12}H_{13}N_4O_2Cl$ requires 281.0800).

Step 2. Preparation of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 385 step 2. ^{1}H NMR (CD_3OD, 400Hz) δ 7.59 (m, 2H), 7.03 (m, 2H), 6.63 (s, 1H), 5.31 (s, 2H), 5.17 (s, 2H), 2.48 (s, 3H), 2.46 (s, 3H); ES-HRMS m/z 407.1097 (M+H $C_{19}H_{17}N_4O_2ClF_2$ requires 407.1081).

Example 388

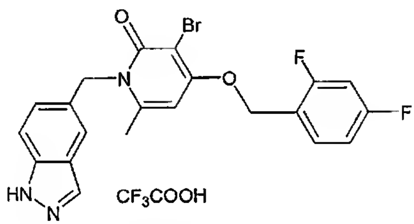


1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

Ion exchange (12.5g) BioRad AG 2X8 resin (200-400 mesh chloride form) was washed with 1M HCl (150 mL), and

equilibrated for 2.5 h. This resin was loaded onto a column, and added a solution of EXAMPLE 387 (1.2 g, 2.4 mmol) in water/CH_3CN (1:1). The column was eluted slowly over 1 h, fractions were collected,and freeze dried to afford the desired HCl salt (1.03 g, 97%) as a white solid: ^1H NMR (CD_3OD, 400Hz) δ 7.60 (m, 2H), 7.04 (m, 2H), 6.64 (s, 1H), 5.31 (s, 2H), 5.17 (s, 2H), 2.50 (s, 3H), 2.47 (s, 3H); ES-HRMS m/z 407.1079 (M+H $C_{19}H_{17}N_4O_2ClF_2$ requires 407.1081).

Example 389

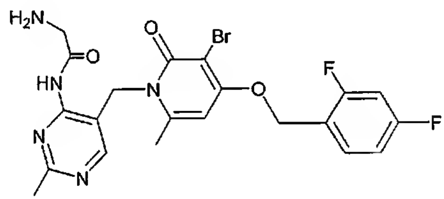


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-ylmethyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.55 g, 0.0017 mol) and 5-(bromomethyl)-1-tetrahydro-2H-pyran-2-yl-1H-indazole (0.5 g, 0.0017 mol) in THF (10.0 mL) was added NaH (0.045 g, 0.0019 m0l) and heated at 60 °C for 16 h under argon atmosphere. THF was distilled under reduced pressure, and the residue was suspended in EtOAc, added acetic acid (0.5 mL) and the product was purified by flash chromatography (80% EtOAc in hexane). The appropriate fractions were combined and concentrated to give an amorphous substance (0.31 g). This was stirred with trifluoroacetic (0.5 mL) for 30 min, the solution was diluted with acetonitrile (5 mL) and the product was isolated by reverse-

phase HPLC using 10 - 90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 460) were combined and freeze dried to afford 0.14 g (52%) of the title compound as its trifluoroacetate salt: ^1H NMR (CD_3OD/400 MHz) δ 7.97 (s, 1H), 7.62 (m, 1H), 7.51 (m, 1H), 7.45 (s, 1H), 7.25 (m, 1H), 7.03 (t, 2H), 6.49 (s, 1H), 5.53 (s, 2H), 5.29 (s, 2H), and 2.40 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ -111.69 (m), -116.09 (m); ES-HRMS m/z 460.0432 (M+H $C_{21}H_{17}N_3O_2BrF_2$ requires 460.0467).

Example 390



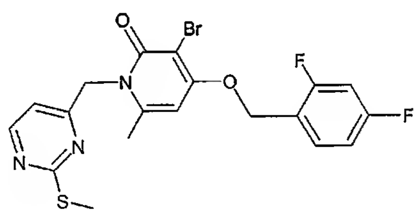
CF_3COOH

N~1~-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinamide trifluoroacetate

To a solution of BOC-Gly-OH (0.19 g, 0.0011 mol) in DMF (2.0 mL), was added N-methylmorpholine (0.14 mL, 0.0011 mol), followed by the addition of isobutylchloroformate (0.15 mL, 0.0011 mol) and stirred at -10 °C for 15 min. Then added a solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate (0/125 g, 0.00022 mol) in DMF (2,0 mL) containing diisopropylethylamine (0.1 g, 0.006 mL) and the resulting mixture was stirred for 16 h, at room temperature. The solvents were distilled in vacuo and the residue was

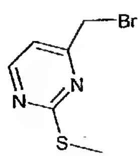
purified by by reverse-phase HPLC using 10 - 90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 608/610) were combined and freeze dried to afford 0.025 g of white powder. This was stirred with trifluoroacetic acid (0.5 mL) for 1 h and product was isolated by reverse-phase HPLC using 10 - 90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 508/510) were combined and freeze dried to afford the title compound (0.02 g) as a white powder: ^1H NMR (CD_3OD/400 MHz) δ 8.18 (s, 1H), 7.61 (m, 1H), 7.02 (m, 2H), 6.59 (s, 1H), 5.30 (s, 4H), 4.23 (s, 2H), 2.60 (s, 3H), and 2.47 (s, 3H); ES-HRMS m/z 508.0797 (M+H $C_{21}H_{21}N_5O_3BrF_2$ requires 508.0790).

Example 391



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-4-yl]methyl}pyridin-2(1H)-one

Step 1



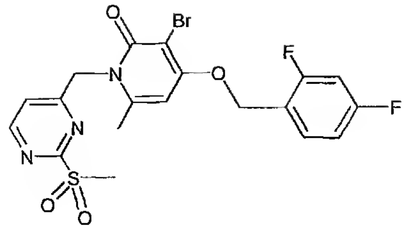
4-(Bromomethyl)-2-(methylthio)pyrimidine

To a solution of 4-methyl-2-methylthiopyrimidine (12.6 g, 0.09 mol) in acetic acid (50.0 mL) was added bromine (5.5 mL, 0.11 mol) and heated at 80 °C under argon atmosphere for 2 h. Acetic acid was distilled in vacuo, the residue was triturated with dichloromethane (100.0 mL) and poured into satd. sod.bicarbonate solution (200.0 mL). Additional dichloromethane (100.0 ml) was added and stirred for 15 min. The organic phase was washed with water (3 x 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The dark colored residue was purified by flash chromatography (EtOAc/hexane 1:4 v/v) to afford 4-(bromomethyl)-2-(methylthio)pyrimidine (10.9 g, 55%) as a dark colored liquid: ^{1}H NMR ($CDCl_3$/400 MHz) δ 8.50 (d, 1H, J = 4.8 Hz), 7.09 (d, 1H, J = 4.8 Hz), 4.34 (s, 2H), and 2.56 (s, 3H); ESMS m/z 219 (M+H).

Step 2

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one 5.0 g, 0.015 mol) and 4-(Bromomethyl)-2-(methylthio)pyrimidine (4.0 g, 0.018 mol) in THF (50.0 mL) was added NaH (0.4 g, 0.0017) and stirred at 55 °C under argon for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between 5% citric acid (25 mL) and EtOAc (50 mL). A precipitate was formed, it was filtered, washed with water, EtOAc, and dried in vacuo to afford the title compound (4.2 g, 59 %) as a light brown powder, ^{1}H NMR (CD_3OD/400 MHz) δ 8.45 (d, 1H, J = 5.2 Hz), 7.6 (m, 1H), 7.06 (d over m, 2H, J = 5.2 Hz), 6.54 (s, 1H), 5.39 (s, 2H), 5.32 (s, 2H), 2.43 (s, 3H), 2.33 (s, 3H); ES-HRMS m/z 468.0173 (M+H $C_{19}H_{17}N_3O_2BrSF_2$ requires 468.0187).

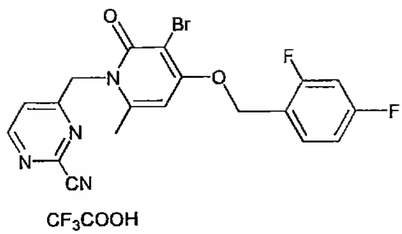
Example 392



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-4-yl]methyl}pyridin-2(1H)-one

A suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-4-yl]methyl}pyridin-2(1H)-one 0.28 g, 0.0006 mol), and magnesium monoperoxyphthalate hexahydrate 90.6 g, 0.0012 mol) in acetonitrile (8.0 ml) and water (2.0 ml) was stirred at room temperature for 16 h. The resulting clear solution was concentrated under reduced pressure, and the residue was partitioned between dichloromethane (30 mL) and water (20 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to afford the title compound (0.27 g, 90%) as a pale yellow substance: ^1H NMR (CD_3OD/400 MHz) δ 8.91 (d, 1H, J = 5.2 Hz), 7.63 (d over m, 2H, J = 5.2 Hz), 7.03 (m, 2H), 6.58 (s, 1H), 5.54 (s, 2H), 5.33 (s, 2H), 3.28 (s, 3H), and 2.49 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ −111.58 (m), -115.98 (m);ES-HRMS m/z 500.0113 (M+H $C_{19}H_{17}N_3O_4BrSF_2$ requires 500.0086).

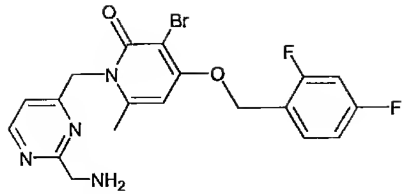
Example 393



4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate

A mixture of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-4-yl]methyl}pyridin-2(1H)-one (1.0 g, 0.002 mol) and NaCN (0.15 g, 0.0031 mol) in DMF (5.0 mL) was stirred at room temperature for 2 h under argon atmosphere. DMF was distilled in vacuo, the residue was triturated with acetonitrile (10 mL) and water (10 mL), and filtered the red colored precipitate. It was washed with acetonitrile and dried to afford the title compound (0.26 g). The washings and the fitrate were combined and purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min to give an additional 0.5 g of the title compound: ^{1}H NMR (CD_3OD/400 MHz) δ 8.83 (d, 1H, J = 5.2 Hz), 7.62 (d over m, 2H, J = 5.2 Hz), 7.00 (m, 2H), 6.58 (s, 1H), 5.46 (s, 2H), 5.33 (s, 2H), and 2.47 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ -111.64 (m), -116.03 (m); ES-HRMS m/z 447.0278 (M+H $C_{19}H_{14}N_4O_2BrF_2$ requires 447.0263).

Example 394

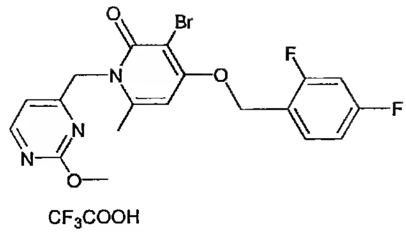


CF_3COOH

4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a solution of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0.3 g. 0.00066mol) in a solvent mixture of EtOAc (15.0 mL) and acetic acid (5.0 mL), was added Pd/C (10 % , 0.18 g) and stirred in an atmosphere of hydrogen at 15 psi for 2 h. The catalyst was removed by filtration . The filtrate was concentrated to dryness and the residue was residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 451) were combined and freeze dried to afford (0.32 g, 645) of the title compound as its trifluoroacetate salt: ^{1}H NMR (DMSO-d_6/400 mHz) δ 8.78 (d, 1H, J = 5.2 Hz), 8.28 (br, 2H), 7.62 (m, 1H), 7.38 (m, 1H), 7.25 (d, 1H, J = 5.2 Hz), 7.18 (m 1H), 6.62 (s, 1H), 5.32 (s, 2H), 5.29 (s, 2H), 4.24 (s, 2H), and 2.46 (s, 3H); ^{19}F NMR (DMSO-d_6/400 MHz) δ − 109.59 (m), -113.67 (m); ES-HRMS m/z 451.0530 (M+H $C_{19}H_{18}N_4O_2BrF_2$ requires 451.0576).

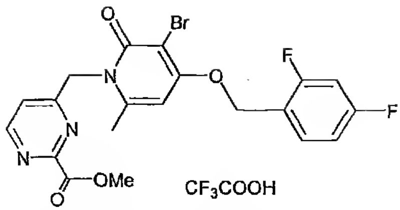
Example 395



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-methoxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

A solution of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0.13 g, 0.00023 mol) in MeOH (2.0 mL) was treated with 1N NaOH (0.5 mL). After stirring at room temperature for 3h, it was heated at 60 °C for an additional 3 h and left overnight room temperature. The resulting solution was diluted with acetonitrile, and purified by reverse-phase HPLC using 10 – 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 452) were combined and freeze dried to afford the title compound (0.015 g) as a white powder: ^1H NMR (CD_3OD) δ 8.84 (d, 1H, J = 5.2 Hz) 7.62 (d, 1H, J = 5.2 Hz), 7.05 (m, 2H), 6.57 (s, 1H), 5.49 (s, 2H), 5.32 (s, 2H), 3.96 (s, 3H), and 2.49 (s, 3H); ES-HRMS m/z 452.0440 (M+H $C_{19}H_{17}N_3O_3BrF_2$ requires 452.0416).

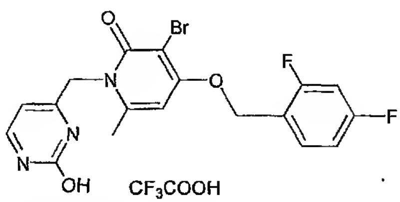
Example 396



Methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carboxylate trifluoroacetate

The title compound was obtained as a second product in the formation of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-methoxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate. ^{1}H NMR (CD_3OD/400 MHz) δ 8.46 (d, 1H, J = 5.2 Hz), 7.62 (m, 1H), 7.00 (m 2H), 6.93 (d, 1H, J = 5.2 Hz), 6.55 (s, 1H), 5.39 (s, 2H), 5.32 (s, 2H), 3.85 (s, 3H), and 2.44 (s, 3H); ES-HRMS m/z 480.0340 (M+H $C_{20}H_{17}N_3O_4BrF_2$ requires 480.0365).

Example 397



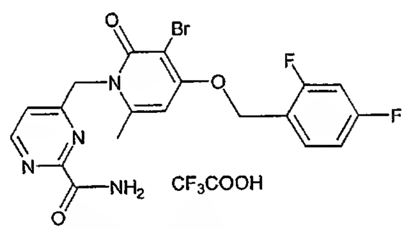
3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-hydroxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

A mixture of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0.2 g, 0.00035 mol) potassium fluoride on

aluminum oxide (0.25 g) in t-butanol (5.0 mL) was refluxed for 4 h under argon atmosphere. The reaction mixture was cooled, filtered the precipitate and washed with ethanol. The combined filtrate and washings were concentrated to dryness and the residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 452) were combined and freeze dried to afford the title compound (0.05 g) as a white powder:

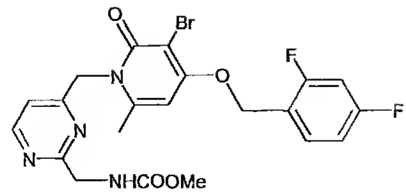
^{1}H NMR (DMSO-d_6/400 Mz) δ 7.85 (d, 1H J = 6.4 Hz), 7.64 (m, 1H), 7.30 (m 1H), 7.15 (m 1H), 6.55 (s, 1H), 6.22 (d, 1H, J = 6.4 Hz), 5.28 (s, 2H), 5.12 (d, 2H), and 2.29 (s, 3H); ^{19}F- NMR (DMSO-d_6/400 MHz) δ - 109.69 (m), and -113.67 (m); ES-HRMS m/z 438.0228 (M+H $C_{18}H_{15}N_3O_3BrF_2$ requires 438.0259).

Example 398



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carboxamide trifluoroacetate

The title compound was obtained by a procedure described for Example 397. ^{1}H NMR (DMSO-d_6/400 MHz) δ 8.82 (d, 1H J = 5.2 Hz), 8.01 (br, 1H), 7.79 (br 1H), 7.64 (m, 1H), 7.34 (m , 2H), 7.16 (m 1H), 6.62 (s, 1H), 5.36 (s, 2H), 5.30 (s, 2H), and 2.38 (s, 3H); ^{19}F NMR (DMSO-d_6/400 MHz) δ - 109.64 (m), and -113.66 (m); ES-HRMS m/z 465.0385 (M+H $C_{19}H_{16}N_4O_3BrF_2$ requires 465.0368).

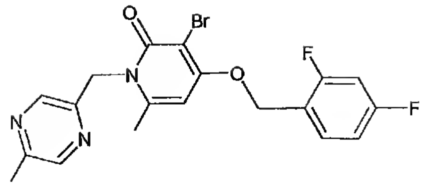


Example 399

Methyl (4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidin-2-yl)methylcarbamate

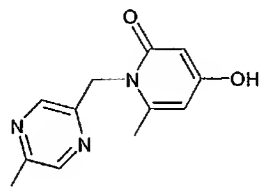
To a solution of 4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.13 g, 0.00023 mol) in dimethylacetamide (1.0 mL), was added triethylamine (0.04 mL, 0.0003 mol), followed by the addition of methylchloroformate (0.05 mL) and stirred at 0 °C for 30 min under argon atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL), The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by flash chromatography (5% MeOH in EtOAc) to afford the title compound (0.055 g, 37%) as pale yellow powder: ^{1}H NMR (DMSO-d_6/400 MHz) δ 8.65 (d, 1H J = 5.6 Hz), 7.63 (1H), 7.5 (m, 1H), 7.28 (m 1H), 7.13 (m, 2H), 6.59 (s, 1H), 5.28 (s, 4H), 5.26 (d, 2H, J = 6.0 Hz), and 2.46 (s, 3H); ^{19}F NMR (DMSO-d_6/400 MHz) δ - 109.64 (m), and -113.71 (m); ES-HRMS m/z 509.0621 (M+H $C_{21}H_{20}N_4O_4BrF_2$ requires 509.0630).

Example 400



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

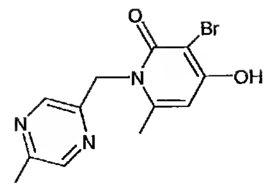
Step 1



4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

A mixture of 4-hydroxy-6-methyl-2-pyrone (5.0 g, 0.04 mol) and 5-aminomethyl-2-methylpyrazine (5.0 g, 0.041 mol) in water (25.0 ml) was heated at 100 °C for 1 h under argon atmosphere. The reaction mixture was cooled, and filtered the yellow precipitate. It was washed with ethanol, and dried in vacuo to afford the title compound (5.8 g, 63%) as a pale yellow powder: ^{1}H NMR (DMSO-d_6/400 MHz) δ 10.43 (br, 1H), 8.38 (d, 2H, J = 5.2 Hz), 5.77 (d, 1H, J = 2.0 Hz), 5.58 (d, 1H, J = 2.0 Hz), 4.92 (s, 2H), 2.24 (s, 3H), and 2.22 (s, 3H); ESMS m/z 232 (M+H).

Step 2



3-Bromo-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

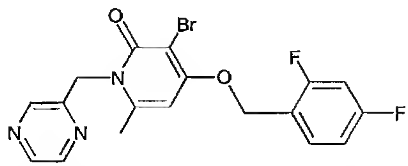
The title compound was prepared by a procedure described in step 2 for Example 385.
Yield: 64%, ^{1}H NMR (CD_3OD/400 MHz) δ 8.47 (s, 1H), 8.42 (s, 1H), 6.07 (s, 1H), 5.38 (s, 2H), 2.51 (s, 3H), and 2.44 (s, 3H), ESMS m/z 310 and 312 (M+H).

Step 3

To a mixture of 3-Bromo-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (0.45 g, 0.0015 mol), and potassium carbonate (0.25 g, 0.0018 mol) in dimethylacetamide (5.0 mL) was added 2,4 difluorobenzyl bromide (0.25 mL. 0.0019 mol)and stirred at room temperature under argon for 1 h. Dimethylacetamide was distilled in vacuo and the residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting material was purified by flash chromatography (EtOAc/hexane 4:1 v/v) as the eluent. The appropriate fractions (m/z = 451/453) were combined and concentrated under reduced pressure to give a white (0.25 g, 38%)solid. ^{1}H NMR (CD_3OD/400 MHz) δ 8.49 (s, 1H), 8.40 (s, 1H), 7.60 (m, 1H), 6.99 (m, 2H), 6.51 (s, 1H), 5.42 (s, 2H), 5.29 (s, 2H), 2.54 (s, 3H), and 2.50 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ −117.70(m), and -

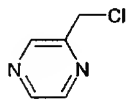
116.09 (m); ES-HRMS m/z 436.0439 (M+H $C_{19}H_{17}N_3O_2BrF_2$ requires 436.0467).

Example 401



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyrazin-2-ylmethyl)pyridin-2(1H)-one

Step 1



2- Chloromethylpyrazine

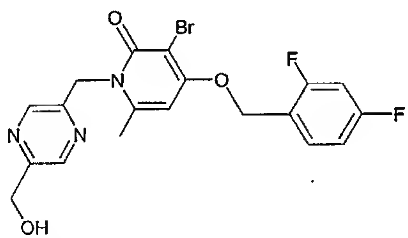
A mixture of 2-methylpyrazine (3.5 g, 0.037 mol), NCS (6.3 g, 0.047 mol) and benzoyl peroxide (0.05 g) was heated to reflux for 16 h under argon atmosphere. It was filtered and the filtrate was concentrated to dryness. The resulting residue was purified by flash chromatography using 30 % EtOAc in hexane to afford 2-chloromethylpyrazine as a dark colored liquid (1.7 g, 36 5): ^{1}H NMR (CD_3OD/400 MHz) δ 8.75 (d, 1H, J = 1.2 Hz), 8.58 (m, 1H), 8.56 (m, 1H), and 4.75 (s, 2H); ESMS m/z = 129 (M+H).

Step 2

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1.8 g, 0.0055 mol) and 2- chloropyrazine (0.8 g, 0.00625) were suspended in THF (25 mL), then added NaH (0.15 g, 0.0062 mol), KI (0.1 g) and the mixture was heated at 65 °C under argon atmosphere for 16 h. The reaction mixture was cooled, added acetic acid (0.5 mL) and concentrated to dryness under reduced pressure. The residue was stirred with a mixture of water (50 mL) and EtoAc (25 mL) and filtered the precipitate. It was washed with water, and acetonitrile an dried in vacuo to afford 1.7 g of light brown powder. ^{1}H NMR (CD_3OD/400 MHz) δ 8.65 (d, 1H), 8.49 (m, 1H), 8.47 9m, 1H), 7.61 (~ q, 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.47 (s, 2H), 5.23 (s, 2H), and 2.53 (s, 3H);

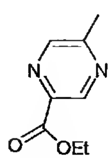
^{19}F NMR (CD_3OD/400 MHz) δ −111.72 (m), and −116.07 (m); ES-HRMS m/z 422.0283 (M+H $C_{18}H_{15}N_3O_2BrF_2$ requires 422.0310).

Example 402



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

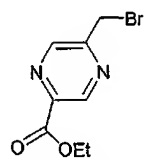
Step 1



Ethyl 5-methylpyrazine-2-carboxylate

A solution of 5-methylpyrazine-2-carboxylic acid (15.0 g, 0.109 mol) in ethanol (70.0 mL) containing (1.5 g, 0.0079 mol) was heated to reflux for 4 h under argon atmosphere. The dark colored solution was cooled, added sod.bicarbonate (1.0 g) and concentrated under reduced pressure. The residue was partitioned between water (50 mL) and EtOAc (100 mL). The organic layer was washed with water (2 x 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford ethyl 5-methylpyrazine-2-carboxylate (12.05 g, 67%) as an orange colored liquid: ^1H NMR (CD_3OD/400 MHz) δ 9.1 (d. 1H, J = 1.2 Hz), 8.62 (d, 1H, J = 1.2 Hz), 4.45 (q, 2H, J = 7.2 Hz), 2.63 (s, 3H), and 1,41 (t, 3H, J = 7.2 Hz); ESMS m/z 167 (M+H).

Step 2

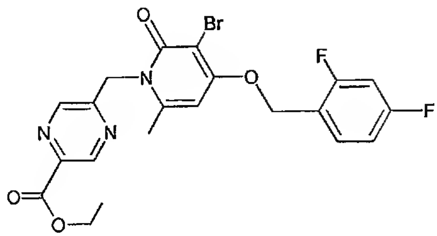


Ethyl 5-(bromomethyl)pyrazine-2-carboxylate

A solution of ethyl 5-methylpyrazine-2-carboxylate (12.0 g, 0.072 mol) in glacial acetic acid (60 mL) containing bromine (4.0 mL) was heated at 80 °C under anhydrous conditions for 45 min. After the removal of acetic acid in vacuo, the residue was partitioned between saturated, bicarbonate (100 mL) and EtOAc (3 x 30 mL). The combined EtOAc extracts were washed with water (2 x 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting liquid was purified by flash chromatography (20 %EtOAc in hexane) to afford ethyl-(5bromomethylpyrazine-2-carboxylate (7.7 g, 44%) as an orange

colored liquid: ^1H NMR (CD_3OD/400 MHz) δ 9.18 (d. 1H, J = 1.2 Hz), 8.85 (d, 1H, J = 1.2 Hz), 4.71 (d, 2H), 4.47 (q, 2H, J = 7.2 Hz), and 1.42 (t, 3H, J = 7.2 Hz); ES-HRMS m/z 244.9942 (M+H $C_8H_{10}N_2O_2Br$ requires 244.9920).

Step 3



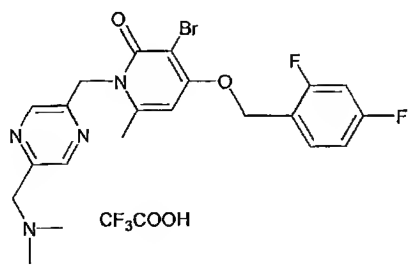
Ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (6.0 g, 0.018 mol) and ethyl 5-(bromomethyl)pyrazine-2-carboxylate (4.9 g, 0.02 mol) in THF (50.0 mL) was added NaH (0.5 g) and heated at 55 °C under argon atmosphere for 3 h. The reaction mixture was cooled , added acetic acid (1.2 ml)and concentrated under reduced pressure. The residue was triturated with water and filtered the solid. It was washed with water, followed by ethanol and dried in vacuo to afford the title compound (3.0 g, 78%)as alight brown powder: ^1H NMR (CD_3OD/400 MHz) δ 9.10 (d. 1H, J = 1.2 Hz), 8.77 (d, 1H, J = 1.2 Hz), 7.61 (m, 1H), 7.01 (m 2H), 6.54 (s, 1H), 5.54 (s, 2H), 5.30 (s, 2H), 4.43 (q, 2H, J = 6.8 Hz), 2.52 (s, 3H), and 1,39 (t, 3H, J = 6.8 Hz); ^{19}F NMR (CD_3OD/400 MHz) δ −111.64(m), and -116.04 (m); ES-HRMS m/z 494.0482 (M+H $C_{21}H_{19}N_3O_4BrF_2$ requires 494.0522).

Step 4

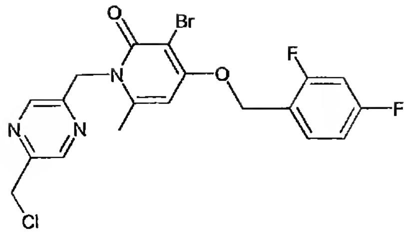
To a suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (2.0 g, 0.004 mol) in t-butanol (15,0 mL and THF (5.0 mL) was added $NaBH_4$ (0.18 g, 0.0047 mol) and the mixture was stirred at room temperature for 16 h under argon atmosphere. It was cooled, added MeOH (5.0 mL) and acetic acid (1.0 mL) and concentrated to dryness . The residue was triturated with water and filtered. It was washed with water, dried in vacuo and purified by flash chromatography (1% MeOH in EtOAc to afford the title compound (0.75 g, 41%) as a pale yellow powder: ^{1}H NMR (CD_3OD/400 MHz) δ 8.58 (d. 1H, J = 1.6 Hz), 8.56 (d, 1H, J = 1.6 Hz), 7.6 (m, 1H), 7.01(m, 2H), 6.52 (s, 1H), 5.46 (s, 2H), 5.29 (s, 2H), 4.71 (s, 2H), and 2.54 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ -111.70(m), and -116.06 (m); ES-HRMS m/z 452.0394 (M+H $C_{19}H_{17}N_3O_3BrF_2$ requires 452.0416).

Example 403



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one trifluoroacetate

Step 1



3-Bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

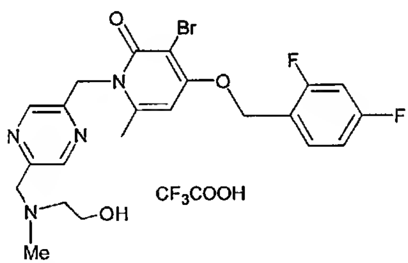
Cyanurylchloride (0.42g, 0.0023 mol) was added to DMF (0.52 mL) and stirred at room temperature for 15 min. Then added dichloromethane (15 mL) followed by the addition of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one 1.0 g, 0.0022 mol) and reaction mixture was stirred at room temperature under argon atmosphere. After 1 h, an additional 1.0 mL of DMF was added and the reaction was allowed to proceed for another hour, when a clear solution was obtained. The solution was diluted with dichloromethane (20 mL) and washed with water, dried (Na_2SO_4), and concentrated to dryness under reduced pressure. The residue was triturated with EtOAc, filtered, washed with EtOAc and dried to afford 0.79 g (77%) of the title compound as a pale yellow powder: ^{1}H NMR (CD_3OD/400MHz) δ 8.66 (s, 2H), 7.73 (m, 1H), 7.05 (m, 2H), 6.56 (s, 1H), 5.52 (s, 2H), 5.33 (s, 2H), 4.74 (s, 2H), and 2.57 (s, 3H); ES-HRMS m/z 470.0051 (M+H $C_{19}H_{16}N_3O_2BrClF_2$ requires 470.0077).

Step 2

A suspension of 3-Bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-

one (0.25 g, 0.00053 mol) in THF (1.0 mL) was treated with N, N,-dimethyl amine (1.0 mL of 2M soln in THF) and stirred at room temperature for 16 h. The reaction mixture was concentrated and the title compound was isolated by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 479) were combined and freeze dried to afford the title compound (0.27 g, 87%) as a white powder: ^{1}H NMR (CD_3OD/400MHz) δ 8.78 (d. 1H, J Hz), 8.56 (d, 1H, J = 1.2 Hz), 7.61 (m 1H), 7.01 (m, 2H), 6.55 (s, 1H), 5.49 (s, 2H), 5.30 (s, 2H), 4.52 (s, 2H), 2.94 (s, 6H) and 2.57 (s, 3H); ^{19}F NMR (CD_3OD) = δ −111.56 (m) and -116.02 (m); ES-HRMS m/z 479.0885 (M+H $C_{21}H_{22}N_4O_2BrF_2$ requires 479.0889).

Example 404

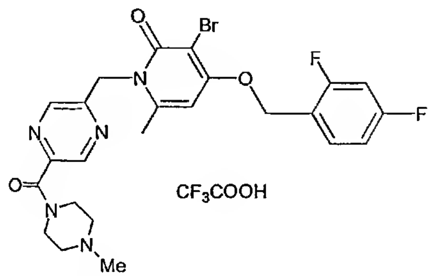


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(2-hydroxyethyl)(methyl)amino]-methyl}pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

The title compound was prepared in a similar manner as described for Example 403, substituting N-methylaminoethanol for N, N-dimethylamine. Yield = 78%, ^{1}H NMR (CD_3OD/400MHz) δ 8.78 (d. 1H, J Hz), 8.59 (d. 1H, J = 1.2 Hz), 7.6 (m, 1H), 7.01 (m, 2H), 6.55 (s, 1H), 5.49 (s,

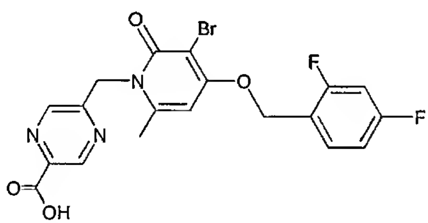
2H), 5.30 (s, 2H), 3.89 (~t, 2H), 2.97 (s, 3H), and 2.57 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) = δ −111.56 (m) and −116.04 (m); ES-HRMS m/z 509.0964 (M+H $C_{22}H_{24}N_4O_3BrF_2$ requires 509.0994).

Example 405



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate

Step 1



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid

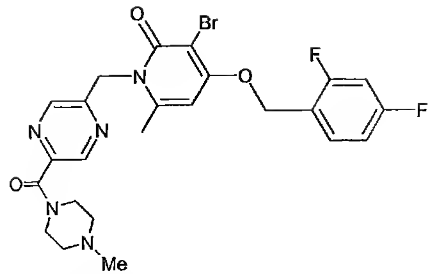
A suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (0.18 g, 0.002 mol) and 1N NaOH (0.6 mL in 1:1 v/v EtOH/Water) was stirred at room temperature for 1.5 h. The reaction mixture was acidified with 5% citric acid and filtered the

precipitate. It was washed with water, followed by ethanol and dried in vacuo to afford the title compound (0.14 g, 77%) as a light brown powder: ^{1}H NMR (CD_3OD/400 MHz) = δ 9.03 (s. 1H), 8.60 (s, 1H), 7.61 (m.1H), 7.00 (m, 2H), 6.52 (s, 1H), 5.51 (s, 2H), 5.30 (s. 2H), and 2.52 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) = δ −111.75 (m) and −116.06 (m); ES-HRMS m/z 466.0209 (M+H $C_{19}H_{15}N_4O_3BrF_2$ requires 466.0209).

Step 2

To a solution of 5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0.28 g, 0.0006 mol) in DMF (3.0 mL), at −15 °C, was added isobutylchloroformate (0.082g, 0.0006 mol), followed by the addition of N-methylmorpholine (0.06 g, 0.00063 mol) and stirred under argon for 15 min. N-methylpiperazine (0.072 g, 0.00072 mol) in DMF (2.0 mL) was then added to the reaction and the mixture was stirred at room temperature for 3 h. After the removal of the solvents in vacuo, the residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 548) were combined and freeze dried to afford the title compound (0.32 g, 80%) as a white powder: ^{1}H NMR (CD_3OD/400 MHz) δ 8.89 (d. 1H, J = 1.6 Hz), 8.73 (d, 1H, J = 1.6 Hz), 7.61 (m, 1H), 7.01 (m,2H), 6.56 (s, 1H), 5.50 (s, 2H), 5.30 (s, 2H), 2.9 (s, 3H), and 2.57 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) = δ - 109.36 (m) and −114.91(m); ES-HRMS m/z 548.1090 (M+H $C_{24}H_{25}N_5O_3BrF_2$ requires 548.1103).

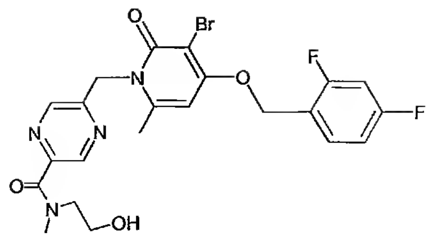
Example 406



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one

A solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate (0.17 g, 0.00026 mol) in 0.1N NaOH (25 mL) was stirred at room temperature for 15 min. and extracted the product in ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL), dried (Na_2SO_4) and concentrated to dryness. The residue was dried in vacuo to afford the title product (0.09 g, 64%) as a white powder: ^{1}H NMR (CD_3OD/400 MHz) δ 8.69 (d. 1H, J = 1.2 Hz), 8.67 (d, 1H, J = 1.2 Hz), 7.60 (m, 1H), 7.00 (m, 2H), 6.54 (s, 1H), 5.50 (s, 2H), 5.30 (s, 2H), 3.78 (t, 2H, J = 4.8 Hz), 3.58 (t, 2H, J = 4.8 Hz), 2.526 (s, 3H), 2.53 (t, 2H, J = 4.8 Hz), 2.44 (t, 2H, J = 4.8 Hz), and 2.31 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) = δ −111.65 (m) and −116.06(m); ES-HRMS m/z 548.1123 (M+H $C_{24}H_{25}N_5O_3BrF_2$ requires 548.1103).

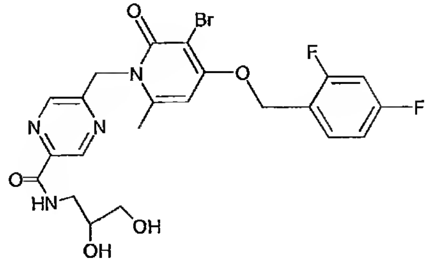
Example 407



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylpyrazine-2-carboxamide

The title compound was prepared in a similar manner as described for Example 405 , substituting N-methylpiperazine by N-methylethanolamine. Yield = 60%,
^{1}H NMR (CD_3OD/400 MHz) δ 8.69 (d. 1H, J = 1.2 Hz), 8.64 (d. 1H, J = 1.2 Hz), 7.61 (m, 1H), 7.00 (m, 2H), 6.54 (s, 1H), 5.49 (s. 2H), 5.30 (s, 2H), 3.81 (~ t, 1H), 3.66 (m, 2H), 3.56 (t, 1H, J = 5.2 Hz), 3.12 (d, 3H J = 7.6 Hz), 2.56 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ -109.64 (m) and -113.66(m); ES-HRMS m/z 523.0743 (M+H $C_{22}H_{22}N_4O_4BrF_2$ requires 523.0797).

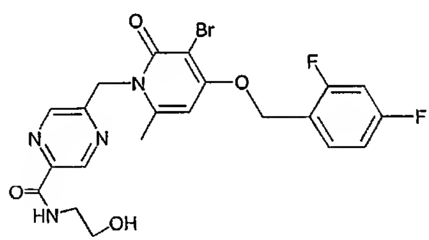
Example 408



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2,3-dihydroxypropyl)pyrazine-2-carboxamide

The title compound was prepared in a similar manner as described for EXAMPLE 405, substituting N-methylpiperazine by 3-amino-1,2-propanediol. Yield = 56%; ^{1}H NMR (CD_3OD/400 MHz) δ 9.09 (d. 1H, J = 1.2 Hz), 8.70 (d. 1H, J = 1.2 Hz), 7.60 (m,1H), 7.00 (m, 2H), 6.54 (s, 1H), 5.53 (s. 2H), 5.30 (s, 2H), 3.80 (m, 1H), 3.61 (dd, 1H), 5.53 (d, 2H), J = 5.2 Hz), 3.42 (dd, 1H), and 2.55 (s, 3H); ^{19}F NMR (CD_3OD/400 MHz) δ −109.65 (m), and −113.67(m); ES-HRMS m/z 539.0703 (M+H $C_{22}H_{22}N_4O_4BrF_2$ requires 539.0736).

Example 409

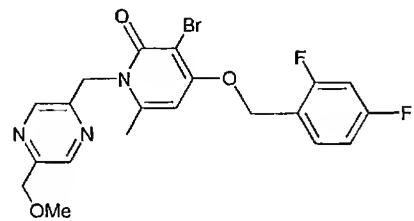


5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)pyrazine-2-carboxamide

The title compound was prepared in a similar manner as described for EXAMPLE 405, substituting N-methylpiperazine by 2-aminoethanol. Yield = 46%; ^{1}H NMR (CD_3OD/400 Hz) δ 9.08 (d. 1H, J = 1.2 Hz), 8.70 (d, 1H, J = 1.2 Hz), 7.601 (m, 1H), 7.01 (m, 2H), 6.54 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 3.69 (t, 2H, J = 6.0 Hz), 3.53 (t, 2H, J = 6.0 Hz), 2.55 (s, 3H);); ^{19}F

NMR (CD_3OD/400 Hz) δ −111.67 (m) and −116.07(m); ES-HRMS m/z 509.0616 (M+H $C_{21}H_{20}N_4O_4BrF_2$ requires 509.0630).

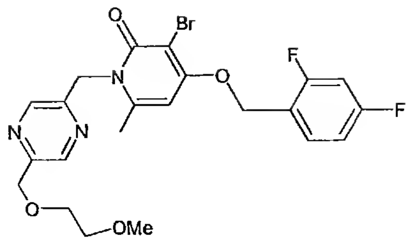
Example 410



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(methoxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0.35 g, 0.00078 mol) in DMF at 0 °C, was added NaH (0.022 g, 0.00092 mol) and stirred for 10 min. Iodomethane (0.05 mL) was added to the reaction and the mixture was stirred at 10 °C for 3 h. DMF was distilled in vacuo and the residue was partitioned between 5% citric acid and EtOAc (15.0 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness. The residue was purified by flash chromatography (EtOAc), and the appropriate fractions were combined and concentrated to a pale yellow powder. ^1H NMR (CD_3OD/400 MHz) δ 8.59 (s), 8.55 (s, 1H), 7.60 (m, 1H), 6.99 (m, 2H), 6.52 (s, 1H), 5.47 (s, 2H), 5.30 (s, 2H), 4.57 (s, 2H), 3.44 (s, 2H), and 2.54 (s, 3H); ^{19}F NMR (CD_3OD/400 Hz) δ −111.69 (m) and −116.09(m); ES-HRMS m/z 466.0577 (M+H $C_{21}H_{19}N_3O_3BrF_2$ requires 466.0572).

Example 411

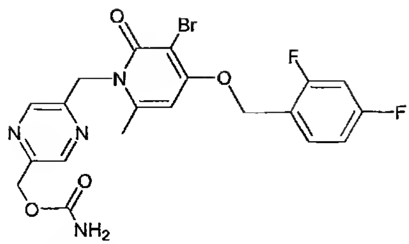


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(2-methoxyethoxy)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one

To a solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0.25 g, 0.00055 mol) in dimethyl acetamide at 0 °C, was added NaH (0.016 g, 0.00067 mol) and stirred for 15 min. 2-Methoxyethyl bromide (0.09 g, 0.00-65 mol) was then added , and the mixture was stirred at room temperature for 6 h. Dimethylacetamide was distilled in vacuo and the product was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 510) were combined and freeze dried to afford the title compound (0.32 g, 80%) as a white powder:

^{1}H NMR (CD_3OD/400 Hz) δ 8.59 (s. 1H), 8.58 (s, 1H), 7.60 (m , 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 4.67 (s, 2H), 3.71 (~t, 2H,), 3.57 (~t, 2H), 3.34 (s, 3H), and 2.54 (s, 3H); ES-HRMS m/z 510.0852 (M+H $C_{20}H_{18}N_4O_4BrF_2$ requires 510.0835).

Example 412

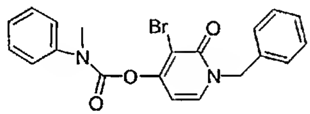


(5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl carbamate

To a suspension of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0.21 g, 0.00055 mol) in THF (5.0 mL) and DMF (2.0 mL), was added 4-nitrophenylchloroformate (0.1 g, 0.0005 mol) and cooled to 0 °C. Triethylamine (0.052g, 0.0005 mol) was then added, stirred at room temperature for 1 h, and at 65 °C for an additional 1h. It was cooled in an ice bath and added 2M ammonia in propanol (1.0 mL) and stirred at room temperature for 2 h. After the removal of the solvents under reduced pressure, the residue was partitioned between 5% sod. bicarbonate, and EtOAc (25 mL). The organic phase was washed with 5% sod. bicarbonate, (3 x 25 mL), water (3 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting substance was purified by isolated by reverse-phase HPLC using 10 -90% CH_3CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 495 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod. bicarbonate (20 mL) and EtOAc (25 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness under reduced pressure, to afford the title compound as a white powder (0.065 g):

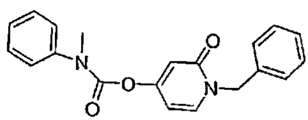
[1]H NMR (CD_3OD/400 MHz) δ 8.61 (br s, 1H), 8.54 (br s, 1H), 7.60)m 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.47 (s, 2H), 5.29 (s, 2H), 5.15 (s, 2H), and 2.54 (s, 3H): [19]F NMR (CD_3OD) δ -111.70 (m), and -116.09 (m); ES-HRMS m/z 495.0449 (M+H $C_{20}H_{18}N_4O_4BrF_2$ requires 495.0474).

Example 413



1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate

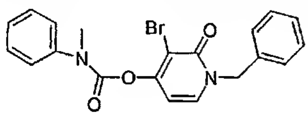
Step 1. Preparation of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate



To a chilled solution of 1-benzyl-4-hydroxypyridin-2(1H)-one (0.375 g, 1.86 mmol) in anhydrous acetonitrile (10 mL) was added triethylamine (0.206 g, 2.04 mmol) followed by N-methyl-N-phenylcarbamoyl chloride (0.379 g, 2.24 mmol). The reaction mixture was stirred under nitrogen atmosphere at 0° C for 30 minutes then at room temperature for 1hour. The reaction was monitored by TLC (5% methanol in dichloromethane). The solvent was removed under reduced pressure and the residue was washed with 10% citric acid and extracted with ethyl acetate. The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under

reduced pressure to afford a yellow syrup. The residue was purified by flash chromatography (silica gel) using 5% MeOH in CH_2Cl_2 to give the desired product (0.382g, 61%) as a white semisolid. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ7.8 (d, 1H, J= 7.2 Hz), 7.39 (m, 10H), 6.19 (s, 2H), 5.03 (s, 2H), 3.29 (s, 3H); ES-HRMS m/z 335.1396 (M+H calculated for $C_{20}H_{19}N_2O_3$ requires 335.1418).

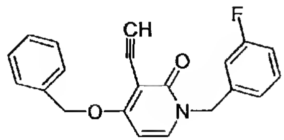
Step 2. Preparation of 1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate



To a solution of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate (0.38 g, 1.13 mmol) in anhydrous CH_2Cl_2 (7 mL) was added N-Bromosuccinimide (NBS, 0.24 g, 1.34 mmol). The reaction was stirred overnight at room temperature under nitrogen atmosphere. The reaction mixture was purified by flash chromatography (silica gel) using ethyl acetate/hexane (1:1 v/v). The appropriate fractions were collected according to ES MS (M+H 413) and concentrated. The dried product showed about 14% of di-bromonated product by analytical HPLC. The compounds were separated by reverse phase HPLC using a 10-90% acetonitrile in water (30 minute gradient) at a 100 mL/min flow rate to afford (after lyophilization) the salt of the desired compound. The salt was diluted in ethyl acetate and washed with $NaHCO_3$. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to afford the desired compound (0.271 g, 58%) as a beige solid. ^{1}H-NMR (d_6-DMSO, 400 MHz) δ7.94 (d, 1H, J= 7.2 Hz), 7.29 (m, 10H), 6.48 (s, 1H),

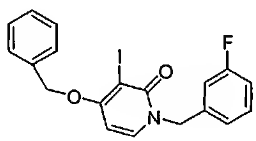
5.12 (s, 2H), 3.33 (s, 3H); ES-HRMS m/z 413.0495 (M+H calculated for $C_{20}H_{18}O_3Br$ requires 413.0496).

Example 414



4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one

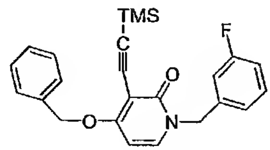
Step 1. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one



A mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4.83 g, 15.6 mmol) in anhydrous acetonitrile (55 mL) and N-iodosuccinimide (NIS, 3.86 g, 17.1 mmol) was heated at 65° C under nitrogen for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel) using ethyl acetate/hexane (1:1 v:v). The appropriate fractions were collected according to ES MS (M+H 436) and washed with Na_2SO_3 to remove the color impurities. The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6.15 g, 90%) as a light yellow solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.73 (d, 1H, J= 7.6 Hz), 7.47 (d, 2H, J= 7.2 Hz), 7.39 (m, 4H), 7.08 (m, 3H), 6.39 (d, 1H,

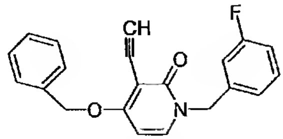
J= 8.0 Hz), 5.29 (s, 2H), 5.19 (s, 2H); ES-HRMS m/z 436.0210 (M+H calculated for $C_{19}H_{16}NO_2FI$ requires 436.0196).

Step 2. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one



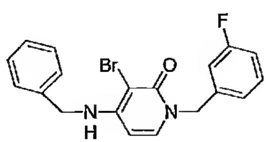
Degassed a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (2.01 g, 4.62 mmol) in anhydrous acetonitrile (25 mL) under argon atmosphere. Triethylamine (1.11 g, 11 mmol) was added and quickly degassed. The reaction mixture was chilled in an ice bath for 15 minutes before adding bistriphenylphosphine-palladium chloride (0.34 g, 0.48 mmol) and cuprous iodide (0.2 g). The reaction was stirred at room temperature for 30 minutes before heating at 60° C under an atmosphere of argon for 2 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure. The dark brown residue was diluted with CH_2Cl_2 (100 mL) and washed with water. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The dark brown residue was purified by flash chromatography using 30% ethyl acetate in hexane. The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (1.34 g, 72%) as a light yellow solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.74 (d, 1H, J= 7.6 Hz), 7.47 (d, 2H, J= 7.6 Hz), 7.35 (m, 4H), 7.09 (m, 3H), 6.46 (d, 1H, J= 7.6 Hz), 5.26 (s, 2H), 5.13 (s, 2H), 0.18 (s, 9H); ES-HRMS m/z 406.1638 (M+H calculated for $C_{24}H_{25}NO_2FSi$ requires 406.1610).

Step 3. Preparation of 4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one



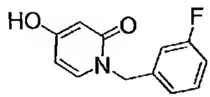
To a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one (1.31 g, 3.2 mmol) in anhydrous acetonitrile (25 mL) at 0° C was added tetrabutylammoniun fluoride (0.611g, 1.93 mmol). The reaction was stirred at 0° C for 15 minutes then for 1 hour at room temperature. The reaction was concentrated under reduced pressure and the residue was diluted with ethyl acetate and washed with water. The organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel) using ethyl acetate in hexane (1:1 v/v). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0.779 g, 72%) as a gold solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.73 (d, 1H, J= 7.6 Hz), 7.43 (d, 2H, J= 7.2 Hz), 7.35 (m, 4H), 7.09 (m, 3H), 6.45 (d, 1H, J= 7.6 Hz), 5.27 (s, 2H), 5.13 (s,2H), 3.78 (s, 1H); ES-HRMS m/z 334.1243 (M+H calculated for $C_{21}H_{17}NO_2F$ requires 334.1234).

Example 415



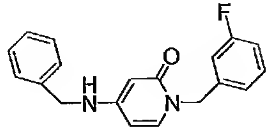
4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one

Step 1. Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one



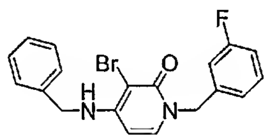
In a Fischer-Porter bottle, added a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4.5 g, 14.56 mmol) in absolute ethanol (20 mL). Flushed the solution with nitrogen then added palladium catalyst (1.05 g, 10% Pd/C). Sealed bottle and evacuated system. The system was purged with hydrogen gas (2 X 15 psi) to check for leaks. The reaction was charged with hydrogen (35 psi) and stirred at room temperature for 45 minutes. The system was evacuated and flushed with nitrogen. The reaction was filtered and the catalyst was carefully washed with fresh ethanol. The filtrate was concentrated under reduced pressure. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.54 (d, 1H, J= 7.6 Hz), 7.32 (m, 1H), 7.06 (d, 1H, J= 7.6 Hz), 6.99 (m, 2H), 6.05 (dd, 1H, J= 2.4 Hz, 2.8 Hz), 5.83 (d, 1H, J= 2.4 Hz), 5.09 (s, 2H); ES-HRMS m/z 220.0774 (M+H calculated for $C_{12}H_{11}NO_2F$ requires 220.0787).

Step 2. Preparation of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one



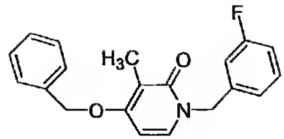
A mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1.005 g, 4.5 mmol) in benzylamine (15 mL) was heated at reflux (185° C) under nitrogen atmosphere for 24 hours. The reaction was monitored by ES-MS (MH+ 309). The solvent was removed by vacuum distillation to give a yellow residue. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.31 (m, 7H), 7.03 (m, 3H), 5.98 (d, 1H, J= 7.2 Hz), 5.45 (s, 1H), 5.00 (s, 2H), 4.30 (s, 2H); ES-HRMS m/z 309.1403 (M+H calculated for $C_{19}H_{18}N_2OF$ requires 309.1375).

Step 3. Preparation of 4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one



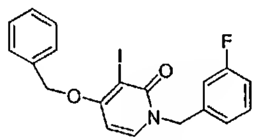
To a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (0.50 g, 1.62 mmol) in anhydrous CH_2Cl_2 (10 mL) was added N-bromosuccinimide (NBS, 0.30 g, 1.7 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 3 hours. The reaction mixture was purified by flash chromatography (silica gel) using ethyl acetate in hexane (1:1 v/v). The appropriate fractions were combined and concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.41 (d, 1H, J= 7.6 Hz), 7.31 (m, 6H), 7.04 (m, 3H), 5.99 (d, 1H, J= 7.6 Hz), 5.08 (s, 2H), 4.53 (s, 2H); ES-HRMS m/z 387.0508 (M+H calculated for $C_{19}H_{17}N_2OBrF$ requires 387.0504).

Example 416



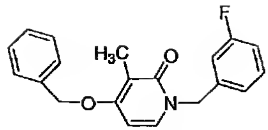
4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1H)-one

Step 1. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one



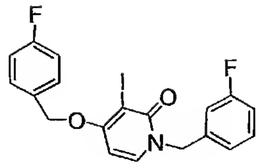
A mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4.83 g, 15.6 mmol) and N-iodosuccinimide (NIS, 3.86 g, 17.1 mmol) in anhydrous acetonitrile (55 mL) was heated at 65° C for 4 hours under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane 1:1 v/v). The appropriate fractions were collected according to ES MS (M+H 436) and washed with Na_2SO_3 to remove the color impurities. The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6.15 g, 90%) as a light yellow solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.73 (d, 1H, J= 7.6 Hz), 7.36 (m, 6H), 7.08 (m, 3H), 6.39 (d, 1H, J= 8.0 Hz), 5.28 (s, 2H), 5.19 (s, 2H); ES-HRMS m/z 436.0196 (M+H calculated for $C_{19}H_{16}NO_2FI$ requires 436.0210).

Step 2. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1H)-one



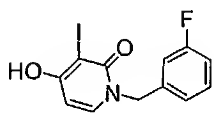
To a degassed solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (1.03 g, 2.36 mmol) in anhydrous DMF (15 mL) under argon atmosphere was added triethylamine (1.11 g, 11 mmol). The reaction mixture was chilled in an ice bath for 15 minutes before adding tetramethyl tin (2.10 g, 11.75 mmol) followed by bistriphenylphosphine-palladium chloride (0.166 g, 0.24 mmol). The reaction was stirred at room temperature for 30 minutes before heating at 95° C under an atmosphere of argon for 3 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure. The dark brown residue was diluted with ethyl acetate (100 mL) and washed with water. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The dark brown residue was purified by flash chromatography (30% ethyl acetate in hexane). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0.1758 g, 22%) as a light yellow solid. The product was further purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 100 mL/min flow rate, to afford a cleaner product as a light yellow solid (0.0975g, 8%). ^{1}H-NMR (CD_3OD, 400 MHz) δ7.58 (d, 1H, J= 7.6 Hz)), 7.35 (m, 6H), 6.98 (m, 3H), 6.46 (d, 1H, J= 7.6 Hz), 5.19 (s, 2H), 5.15 (s, 2H), 2.0 (s, 3H); ES-HRMS m/z 324.1366 (M+H calculated for $C_{20}H_{19}NO_2F$ requires 324.1394).

Example 417



1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one

Step 1: Preparation of 1-(3-fluorobenzyl)-4-hydroxy-3-iodopyridin-2(1H)-one



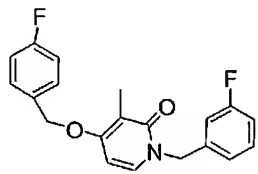
To a mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1.1 g, 5 mmol) in acetonitrile (15 mL) was added N-iodosuccinimide (1.1 g, 5.5 mmol) along with a ca. amount of dichloroacetic acid (0.1 mL). The reaction mixture stirred at room temperature for 1 hour under nitrogen. The mixture was chilled in an ice bath and filtered cold with fresh $MeCl_2$. The beige solid was dried to afford the desired iodinated intermediate (1.21g, 69%). ES-LRMS m/z 346.

Step 2: Preparation of 1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one

To a mixture of 1-(3-fluorobenzyl)-4-hydroxy-3-iodopyridin-2(1H)-one (0.5g, 1.44 mmol) in DMF (5 mL) was added K_2CO_3 (0.199g, 1.44 mmol) followed by the addition of 4-fluorobenzyl bromide (0.189 mL, 1.51 mmol). The reaction

mixture stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate (50 mL) and washed with water. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. ^{1}H-NMR (CD_3OD, 400 MHz) δ7.75 (d, 1H, J= 7.6 Hz), 7.49 (q, 2H), 7.34 (q, 1H), 7.11(m, 5H), 6.40 (d, 1H, J= 7.6 Hz), 5.26 (s, 2H), 5.19 (s, 2H); ES-HRMS m/z 454.0098 (M+H calculated for $C_{19}H_{15}NO_2F_2I$ requires 454.0110).

Example 418

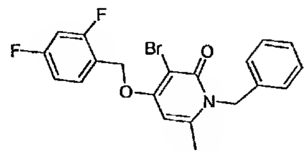


1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-methylpyridin-2(1H)-one

To a degassed solution of 1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one (0.804g, 1.7 mmol) in DMF (10 mL) and LiCl (0.25g, 5.9 mmol) was added tetramethyltin (0.49 mL, 3.54 mmol) followed by bistriphenylphosphine-palladium chloride catalyst (0.124g, 0.177 mmol). The reaction mixture was heated in an oil bath (85°-90° C) under nitrogen for 3 hours. The solvent was concentrated and the residue was diluted with ethyl acetate and washed with water. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash column chromatography (20% ethyl acetate in hexane). The appropriate fractions were concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.59 (d, 1H, J=7.6 Hz), 7.46 (m, 2H), 7.34 (m, 1H), 7.10 (m, 4H), 6.46 (d, 1H, J=7.6 Hz), 5.17 (s, 2H),

5.15 (s, 2H), 1.99 (s, 3H); ES-HRMS m/z 342.1314 (M+H calculated for $C_{20}H_{18}NO_2F_2$ requires 342.1300).

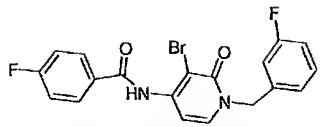
Example 419



1-benzyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

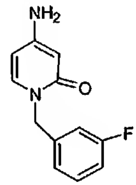
To a degassed cold solution of DMF (10 mL) and PPh_3 (resin, 0.93 g, 2.75 mmol) was added DEAD (0.44 mL, 2.75 mmol). The reaction mixture stirred at -10°C for 20 minutes under nitrogen. A solution of 1-benzyl-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one (0.62 g, 2.1 mmol) and 2,4-difluorobenzylalcohol (0.283 mL, 2.5 mmol) in DMF (10 mL) was added to the resin suspension. The reaction mixture stirred at -10° C for 30 minutes and then allowed to stir at room temperature for 1 hour. The resin was filtered and rinsed with fresh MeOH and the filtrate was concentrated. The residue was dissolved in ethyl acetate and purified by flash column chromatography (ethyl acetate/hexane 1:1 v/v). The appropriate fractions were concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.62 (m, 1H), 7.31 (m, 3H), 7.1 (d, 2H, J= 7.2 Hz), 7.02 (t, 2H, J= 8.6 Hz), 6.48 (s, 1H), 5.42 (s, 2H), 5.28 (s, 2H), 2.34 (s, 3H); ES-HRMS m/z 420.0399/422.0380 (M+H calculated for $C_{20}H_{17}NO_2F_2Br$ requires 420.0405/422.0387).

Example 420



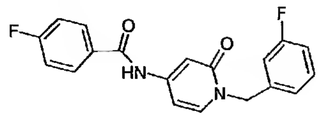
N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide

Step 1. Preparation of 4-amino-1-(3-fluorobenzyl)pyridin-2(1H)-one



In a Fischer-Porter bottle, added a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (2.5g, 8.11 mmol) in glacial acetic acid (20 mL). After the solution was flushed with nitrogen, catalyst was added (10%Pd/C, 2.0g). The vessel was sealed, evacuated, and purged with hydrogen gas. The system was charged with hydrogen gas (50psi) and the mixture stirred at room temperature for 4 hours. The system was evacuated and flushed with nitrogen. The reaction mixture was filtered through a bed of celite and washed with fresh ethanol. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate 3:4 v/v). The filtrate was concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.32 (q, 1H), 7.02 (m, 3H), 5.93 (dd, 1H, J= 2.4 Hz, 2.8 Hz), 5.58 (d, 1H, J= 2.4 Hz); ES-HRMS m/z 219.0966 (M+H calculated for $C_{12}H_{12}N_2OF$ requires 219.0928).

Step 2. Preparation of 4-fluoro-N-[1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzamide

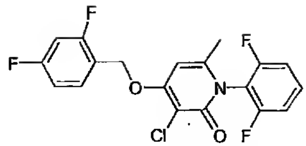


To a solution of 4-amino-1-(3-fluorobenzyl)pyridin-2(1H)-one (0.263 g, 1.2 mmol) in acetonitrile (7 mL) was added a DMAP (ca.), triethylamine (0.25 mL, 1.8 mmol) and 4-fluorobenzoyl chloride (0.213 mL, 1.8 mmol). The reaction mixture stirred at 0° C for 25 minutes and then filtered. The solid was washed with 10% citric acid and water to afford the desired compound (0.326 g, 79%) after drying. ^{1}H-NMR (d_6DMSO, 400 MHz) δ 7.98 (m, 2H), 7.71 (d, 1H, J= 7.6 Hz), 7.35 (m, 3H), 7.08 (m, 3H), 6.98 (d, 1H, J= 2.4 Hz), 6.61 (dd, 1H, J= 2.4 Hz, 2.4 Hz), 5.03 (s, 2H); ESLRMS m/z 341.1.

Step3. Preparation of N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide

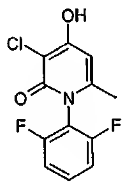
To a mixture of 4-fluoro-N-[1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzamide (0.305g, 0.89 mmol) in acetonitrile (7 mL) was added NBS (0.159g, 0.89 mmol). The reaction mixture stirred at room temperature for 1.5 hours. The filtrate was removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate/hexane 1:1 v/v). The fractions were concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.03 (m, 2H), 7.79 (d, 1H, J= 7.6 Hz), 7.47 (d, 1H, J= 8.0 Hz), 7.28 (m, 3H), 7.12 (m, 3H), 5.23 (s, 2H); ES-HRMS m/z 419.0202/421.0191 (M+H calculated for $C_{19}H_{14}N_2O_2F_2Br$ requires 419.0201/421.0183).

Example 421



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1. Preparation of 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



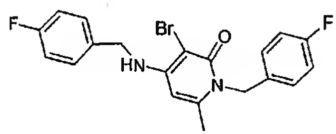
To a mixture of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.30 g, 1.26 mmol) in dichloromethane (5 mL) was added NCS (2.52 g, 1.90 mmol). The reaction mixture stirred at room temperature under nitrogen for 4.5 hours. The suspension was cooled in ice bath, filtered, and the solid was rinsed with fresh dichloromethane to afford the desired product (0.271 g, 79%) as a white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.58 (m, 1H), 7.22 (m, 2H), 6.20 (s 1H), 2.00 (s, 3H); ES-HRMS m/z 272.0287 (M+H calculated for $C_{12}H_9NO_2F_2Cl$ requires 272.0290).

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

To a solution of 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.27 g, 1.00 mmol) in DMA

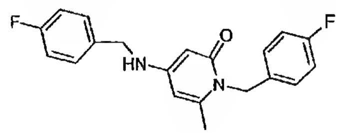
(5 mL) was added K_2CO_3 followed by the addition of 2,4-difluorobenzyl bromide (0.128 mL, 1 mmol). The reaction mixture stirred at room temperature for 2 hours and then was diluted in water. The reaction mixture was extracted with ethyl acetate, the organic extracts were dried over Na_2SO_4 and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 3:4 v/v) to afford the desired product. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.60 (m, 2H), 7.25 (m, 2H), 7.04 (m, 2H), 6.71 (s, 1H), 5.36 (s, 2H), 2.11 (s, 3H); ES-HRMS m/z 398.0551 (M+H calculated for $C_{19}H_{13}NO_2F_4Cl$ requires 398.0571).

Example 422



3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one



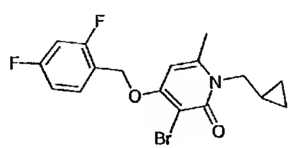
A mixture of 4-hydroxy-6-methylpyrone (5.0 g, 0.04 mol) and 4-fluorobenzylamine (10.0 g. 0.08 mol) in n-butanol (25.0 mL) was heated to reflux for 24 hours under argon atmosphere. The resulting solution was concentrated to dryness under reduced pressure. The residue was triturated with ethyl acetate and filtered. It was thoroughly washed with ethyl

acetate and dried to afford the title compound as a pale yellow powder (4.1 g. 30%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.33 (q, 2H), 7.04 (m, 5H), 5.85 (d, 1H, J= 2.0 Hz), 5.44 (d, 2H, J= 2.4 Hz), 5.20 (s, 1H), 4.29 (s, 2H), 2.17 (s, 3H); ES-HRMS m/z 341.1488 (M+H calculated for $C_{20}H_{19}N_2OF_2$ requires 341.1460).

Step 2: Preparation of 3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one

To a solution of 1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one (0.2857 g, 0.84 mmol) in $MeCl_2$ was added NBS (0.156 g, 0.88 mmol). The reaction stirred at room temperature under nitrogen for 45 minutes. The reaction mixture was diluted with $MeCl_2$ and washed with $NaHCO_3$. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated to afford the desired product (0.3242 g, 92%) as a yellow solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.32 (q, 2H), 7.04 (m, 6H), 5.91 (s, 1H), 5.28 (s, 2H), 4.50 (s, 2H), 2.17 (s, 3H); ES-HRMS m/z 419.0549/421.0537 (M+H calculated for $C_{20}H_{18}N_2OBrF_2$ requires 419.0565/421.0547).

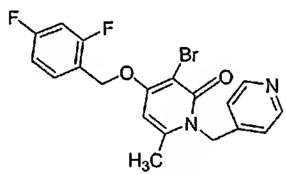
Example 423



3-bromo-1-(cyclopropylmethyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

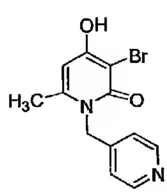
To a mixture of 3-bromo-1-(cyclopropylmethyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.276 g, 1.07 mmol) and K_2CO_3 (0.148 g, 1.07 mmol) in DMA (4 mL) was added 2, 4-difluorobenzyl bromide (0.14 ml, 1.07 mmol). The mixture stirred at room temperature for 1.5 hours. The reaction mixture was diluted in water and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:1 v/v). The appropriate fractions were combined, and concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.60 (q, 1H), 7.04 (m, 2H), 6.42 (s, 1H), 5.26 (s, 2H), 4.06 (s, 1H), 4.04 (s, 1H), 2.50 (s, 3H), 0.53 (m, 2H), 0.43 (m, 2H); ES-HRMS m/z 384.0392 (M+H calculated for $C_{17}H_{17}N_2OBrF_2$ requires 384.0405).

Example 424



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

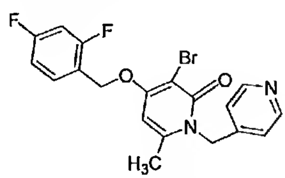
Step 1. Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



Commercially available 4-hydroxy-6-methyl pyrone (10 g, 79.3 mmol) was condensed with commercially available 4-(aminomethyl) pyridine (8 mL, 79.3 mmol) in water (50mL). The mixture was heated in an oil bath at reflux for 1 hour under nitrogen. The solvent was evaporated. MS and ^{1}H-NMR were consistent with the desired desbrominated structure. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (dd, 2H, J= 1.6 Hz,1.6 Hz), 7.15 (d, 2H, J= 6.0 Hz), 6.00 (d, 1H, J= 2.0 Hz), 5.80 (d, 1H, J= 2.4 Hz), 5.34 (s, 2H), 2.23 (s, 3H); ES-LRMS (M+H) m/z 217.

To a suspension of the above compound (0.801 g, 3.7 mmol) in $MeCl_2$ (10 mL) was added NBS (0.725 g, 4.07 mmol). The reaction mixture stirred at room temperature for 30 minutes under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh $MeCl_2$ and dried to afford a beige solid (0.9663 g, 88%) after drying. ^{1}H-NMR (CD_3OD, 400 MHz) δ8.47 (d, 2H, J= 5.2 Hz), 7.16 (d, 2H, J= 6.0 Hz), 6.09 (s, 1H), 5.40 (s, 2H), 2.24 (s, 3H); ES-LRMS (M+H) m/z 295/297.

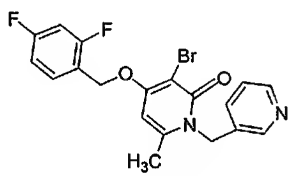
Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



To a cold solution of 2,4-difluorobenzylalcohol (0.569 mL, 5.1 mmol) in THF (5 mL) was added PPh_3 (resin, 2.55 g, 7.65 mmol) followed by the addition of DIAD (1.48 mL, 7.65 mmol). The reaction mixture stirred at -10°C for 15 minutes under nitrogen. A solution of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one (1.0 g, 3.4 mmol), in DMF (10 mL) was added to the resin suspension. The reaction

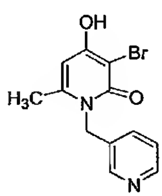
mixture stirred at 0° C for 1.5 hours and then allowed to stir at room temperature overnight. The resin was filtered and rinsed with fresh MeOH and the filtrate was concentrated. The residue was dissolved in ethyl acetate and purified by flash column chromatography (ethyl acetate). The appropriate fractions were concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.47 (d, 2H, J= 5.6 Hz), 7.63 (q, 1H), 7.15 (d, 1H, J= 5.6 Hz), 7.05 (m, 2H), 6.55 (s, 1H), 5.45 (s, 2H), 5.31 (s, 2H), 2.35 (s, 3H); ES-HRMS m/z 421.0366/423.0355 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Br$ requires 421.0358/423.0339).

Example 428



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

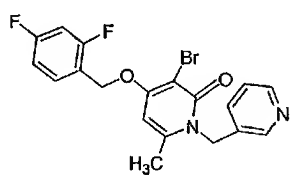


Commercially available 4-hydroxy-6-methyl pyrone (15 g, 119.0 mmol) was condensed with commercially available 3-(aminomethyl) pyridine (12.10 mL, 119.0 mmol) in water (75

mL). The mixture was heated in an oil bath at reflux for 1 hour under nitrogen. The solvent was evaporated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.43 (d, 1H, J= 4.8 Hz), 8.38 (s, 1H), 7.60 (d, 1H, J= 8.0 Hz), 7.39 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 5.97 (d, 1H, J= 2.0 Hz), 5.79 (d, 1H, J= 2.4 Hz), 5.33 (s, 2H), 2.28 (s, 3H); ES-LRMS (M+H) m/z 217.

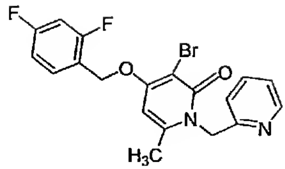
To a suspension of the above compound (5.01 g, 23.1 mmol) in $MeCl_2$ (50 mL) was added NBS (4.53 g, 25.4 mmol). The reaction mixture stirred at room temperature for 30 minutes under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh $MeCl_2$ and dried to afford a beige solid (7.89 g, 114%) after drying. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.44 (d, 1H, J= 4.4 Hz), 8.39 (s, 1H), 7.62 (d, 1H, J= 7.6 Hz), 7.39 (dd, 1H, J= 5.2 Hz, 4.4 Hz), 6.07 (s, 1H), 5.39 (s, 2H), 2.29 (s, 3H); ES-LRMS (M+H) m/z 295/297.

Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



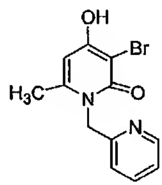
The compound was prepared essentially as described in Step 2 of example 424 using 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 8.41 (s, 1H), 7.63 (m, 2H), 7.41 (dd, 1H, J= 5.2 Hz, 4.8 Hz), 7.02 (m, 2H), 6.52 (s, 1H), 5.44 (s, 2H), 5.29 (s, 2H), 2.40 (s, 3H); ES-HRMS m/z 421.0355/423.0358 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Br$ requires 421.0358/423.0339).

Example 435



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one

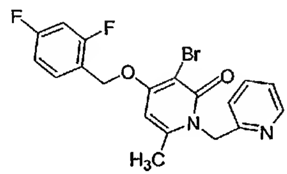


Commercially available 4-hydroxy-6-methyl pyrone (5 g, 39.6 mmol) was condensed with commercially available 2-(aminomethyl) pyridine (4.03 mL, 39.6 mmol) in water (25 mL). The mixture was heated in an oil bath at reflux for 1.5 hour under nitrogen. The solvent was evaporated. MS and ^{1}H-NMR were consistent with the desired desbromonated structure. ^{1}H-NMR (CD_3OD, 400 MHz) δ8.47 (d, 1H, J= 4.8 Hz), 7.75 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.28 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.11(d, 1H, J= 7.6 Hz), 5.98 (d, 1H, J= 2.4 Hz), 5.77 (d, 1H, J= 2.4 Hz), 5.35 (s, 2H), 2.28 (s, 3H); ES-LRMS (M+H) m/z 217.

To a suspension of the above compound (3.0 g, 13.8 mmol) in $MeCl_2$ (30 mL) was added NBS (2.71 g, 15.18 mmol). The reaction mixture stirred at room temperature for 2.5 hours under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh $MeCl_2$ and dried to afford a beige solid (3.18 g, 77%) after drying. ^{1}H-NMR

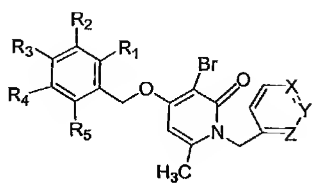
(CD_3OD, 400 MHz) δ 8.46 (d, 1H, J= 4.8 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.29 (dd, 1H, J= 5.2 Hz, 5.2 Hz), 7.17 (d, 1H, J= 8.0 Hz), 6.07 (s, 1H), 5.40 (s, 2H), 2.30 (s, 3H); ES-LRMS (M+H) m/z 295/297.

Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one



The compound was prepared essentially as described in Step 2 of example 424 using 3-bromo-4-hydroxy-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 2.0 Hz, 1.6 Hz), 7.62 (q, 1H), 7.29 (dd, 1H, J= 5.2 Hz, 5.6 Hz), 7.21 (d, 1H, J= 8.0 Hz), 7.04 (m, 2H), 6.51 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.42 (s, 3H); ES-HRMS m/z 421.0354/423.0332 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Br$ requires 421.0358/423.0339).

Examples 425-427, 429-435, 436-437



The following compounds were prepared essentially according to the procedures set forth above for Example 424, using the products of Step 1 of Examples 424, 428, or 435.

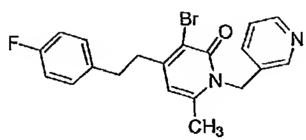
Ex.No.	R_1	R_2	R_3	R_4	R_5	X	Y	Z	MF	M+H m/z required	ES-HRMS m/z
425	H	H	F	H	H	N	CH	CH	$C_{19}H_{16}N_2O_2FBr$	403.0452/ 405.0434	403.0444 405.0414
426	F	H	F	H	F	N	CH	CH	$C_{19}H_{14}N_2O_2F_3Br$	439.0264/ 441.0245	439.0270 441.0274
427	F	H	H	H	F	N	CH	CH	$C_{19}H_{15}N_2O_2F_2Br$	421.0358/ 423.0339	421.0378 423.0368
429	H	H	F	H	H	CH	N	CH	$C_{19}H_{16}N_2O_2FBr$	403.0487/ 405.0438	403.0487 405.0438
430	F	H	F	H	F	CH	N	CH	$C_{19}H_{14}N_2O_2F_3Br$	439.0264/ 441.0245	439.0267 441.0241
431	F	H	H	H	H	CH	N	CH	$C_{19}H_{16}N_2O_2FBr$	403.0452/ 405.0434	403.0489 405.0474
432	F	H	F	F	H	CH	N	CH	$C_{19}H_{14}N_2O_2F_3Br$	439.0264/ 441.0245	439.0266 441.0231
433	F	H	Cl	H	H	CH	N	CH	$C_{19}H_{15}N_2O_2FClBr$	437.0062/ 439.0041	437.0068 439.0041
434	Cl	H	F	H	H	CH	N	CH	$C_{19}H_{15}N_2O_2FClBr$	437.0062/ 439.0041	437.0048 439.0043
435	F	H	H	H	F	CH	N	CH	$C_{19}H_{15}N_2O_2F_2Br$	421.0358/ 423.0339	421.0371 423.0336
436	H	H	F	H	H	CH	CH	N	$C_{19}H_{16}N_2O_2FBr$	403.0452/ 405.0434	403.0454 405.0379
437	F	H	F	H	F	CH	CH	N	$C_{19}H_{14}N_2O_2F_3Br$	439.0264/ 441.0245	439.0266 441.0242
438	F	H	F	F	H	CH	CH	N	$C_{19}H_{14}N_2O_2F_3Br$	439.0264/ 441.0245	439.0264 441.0241

NMR characterization of compounds of Examples 425-427, 429-435, 436-437

Ex.No.	NMR Data
425	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.47 (d, 2H, J= 5.6 Hz), 7.50 (q, 2H), 7.14 (m, 4H), 6.49 (s, 1H), 5.44 (s, 2H), 5.27 (s, 2H), 2.32 (s, 3H
426	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.48 (dd, 2H, J= 1.6 Hz), 7.15 (d, 2H, J= 6.0 Hz), 6.98 (t, 2H, J= 1.2 Hz), 6.60 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.36 (s, 3H)

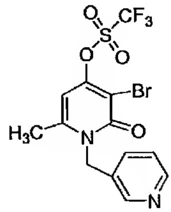
427	^{1}H NMR (CD_3OD, 400 MHz) δ 8.47 (d, 2H, J = 1.6 Hz), 7.45 (m, 1H), 7.16 (d, 2H, J = 5.6 Hz), 7.06 (t, 2H, J = 8.4 Hz), 6.62 (s, 1H), 5.46 (s, 2H), 5.34 (s, 2H), and 2.37 (s, 3H)
429	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 8.40 (s, 1H), 7.62 (d, 1H, J= 8.0 Hz), 7.49 (q, 2H), 7.41 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.14 (t, 2H, J= 8.8 Hz), 6.46 (s, 1H), 5.43 (s, 2H), 5.26 (s, 2H), 2.38 (s, 3H)
430	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 3.6 Hz), 8.42 (d, 1H, J= 1.2 Hz), 7.60 (d, 1H, J= 8.4 Hz), 7.41 (dd, 1H, J= 5.2 Hz, 4.8 Hz), 6.97 (m, 2H), 6.57 (s, 1H), 5.45 (s, 2H), 5.27 (s, 2H), 2.42 (s, 3H)
431	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 8.41 (d, 1H, J= 1.6 Hz), 7.58 (m, 2H), 7.41 (m, 2H), 7.22 (m, 2H), 6.51 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 2.39 (s, 3H)
432	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.41 (d, 1H, J=1.6 Hz), 7.63 (d, 1H, J= 7.6 Hz), 7.53 (m, 1H), 7.41 (dd, 1H, J= 5.6 Hz, 5.2 Hz), 7.26 (m, 1H), 6.51 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.40 (s, 3H)
433	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.41 (d, 1H, J= 1.6 Hz), 7.60 (m, 2H), 7.39 (dd, 1H, J= 5.2 Hz), 7.28 (s, 1H), 7.26 (s, 1H), 6.50 (s, 1H), 5.44 (s, 2H), 5.31 (s, 2H), 2.40 (s, 3H)
434	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.41 (d, 1H, J= 1.6 Hz), 7.68 (m, 2H), 7.39 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.31 (dd, 1H, J= 2.4 Hz, 2.8 Hz), 7.16 (ddd, 1H, J= 2.8 Hz, 2.8 Hz, 2.8 Hz), 6.50 (s, 1H), 5.45 (s, 2H), 5.32 (s, 2H), 2.41 (s, 3H)
435	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.42 (s, 1H), 7.60 (d, 1H, J= 8.0 Hz), 7.47 (m, 1H), 7.40 (dd, 1H, J= 5.2 Hz, 4.8 Hz), 7.07 (m, 2H), 6.59 (s, 1H), 5.45 (s, 2H), 5.32 (s, 2H), 2.41 (s, 3H)
436	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.8 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.51 (q, 2H), 7.30 (dd, 1H, J= 5.2 Hz), 7.19 (d, 1H, J= 7.6 Hz), 7.14 (t, 2H, J= 8.8 Hz), 6.46 (s, 1H), 5.44 (s, 2H), 5.26 (s, 2H), 2.40 (s, 3H)
437	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H, J= 4.8 Hz), 7.76 (ddd, 1H, J=2.0 Hz, 1.6 Hz, 1.6 Hz), 7.29 (dd, 1H, J= 4.8 Hz, 5.2 Hz), 7.21 (d, 1H, J= 7.6 Hz), 6.69 (dd, 2H, J= 8.0 Hz, 7.6 Hz), 6.57 (s, 1H), 5.46 (s, 2H), 5.28 (s, 2H), 2.43 (s, 3H)
438	^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.55 (m, 1H), 7.26 (m, 3H), 6.50 (s, 1H), 5.46 (s, 2H), 5.29 (s, 2H), 2.42 (s, 3H)

Example 439



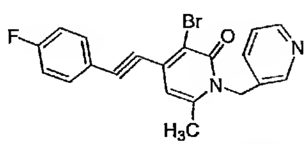
3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-bromo-6-methyl-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl trifluoromethanesulfonate



To a chilled suspension (-30° C) of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (0.481g, 1.63 mmol) in dichloromethane (6 mL) was added triethylamine (0.28 mL, 2.04 mmol), followed by the addition of a solution of trifluoromethanesulfonic anhydride (0.4 mL, 2.44 mmol) in dichloromethane (3 mL). The reaction mixture stirred at -30° C under nitrogen for 1 hour. The reaction mixture was diluted with dichloromethane and washed with cold $NaHCO_3$/water. The organic extracts were dried over Na_2SO_4 and the filtrate was concentrated under reduced pressure to afford the desired compound as a yellow semisolid (0.6675 g, 95%) after drying. ES-LRMS (M+H) m/z 427.1/429.1.

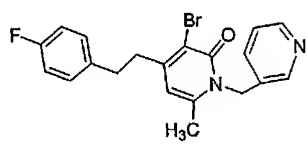
Step 2. Preparation of 3-bromo-4-[(4-fluorophenyl)ethynyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



To a degassed solution of 3-bromo-6-methyl-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (0.6675 g, 1.56 mmol) in DMF (9 mL),

DIEA (0.35 mL, 2.03 mmol), 4-fluorophenylacetylene (0.235 mL, 1.95 mmol) and $PdCl_2(PPh_3)_2$ (0.11g) were added. The reaction mixture stirred at room temperature under nitrogen for 1 hour and then heated in an oil bath (65°C) under nitrogen overnight. The solvents were distilled in vacuo and the residue was purified by flash column chromatography (5% methanol in ethyl acetate). The extracts were concentrated to afford the desired compound (0.432 g, 69%) after drying. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (s, 2H), 7.96 (s, 1H), 7.64 (m, 3H), 7.41 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.18 (t, 2H, J= 8.8 Hz), 6.46 (s, 1H), 5.45 (s, 2H), 2.37 (s, 3H); ES-HRMS m/z 397.0361/399.0310 (M+H calculated for $C_{20}H_{15}N_2OFBr$ requires 397.0346/399.0328).

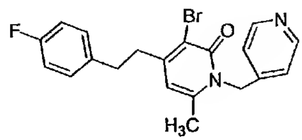
Step 3. Preparation of 3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



A suspension of 3-bromo-4-[(4-fluorophenyl)ethynyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (0.430 g, 1.01 mmol) in Ethyl acetate (5 mL) and EtOH (5 mL), containing PtO_2 (0.015 g) was stirred in an atmosphere of hydrogen (15 psi) in a Fischer- Porter bottle for 2 hours. The reaction mixture was filtered and the filtrate was concentrated to reduce volume. The material was purified by flash column chromatography (ethyl acetate). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0.0943 g, 22 %) as a sticky semisolid after drying. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.46 (d,

2H, J= 26.4 Hz), 7.60 (d, 1H, J= 8.0 Hz), 7.41 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.21 (m, 2H), 6.97 (t, 2H, J= 8.8 Hz), 6.24 (s, 1H), 5.43 (s, 2H), 2.93 (m, 4H), 2.31 (s, 3H); ES-HRMS m/z 401.0645/403.0603 (M+H calculated for $C_{20}H_{19}N_2OFBr$ requires 401.0659/403.0641).

Example 440

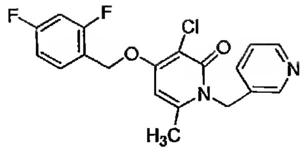


3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for step 1 to step3 (0.374 g, 25%). MS and ^{1}H-NMR for step 1 were consistent with the desired structure. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.80 (d, 2H, J= 6.8 Hz), 7.89 (d, 2H, J= 6.8 Hz), 6.61 (s, 1H), 5.66 (s, 2H), 2.45 (s, 3H); ES-HRMS m/z 427.9645/429.9625 (M+H calculated for $C_{13}H_{11}N_2O_4SF_3Br$ requires 427.9599/429.9578).

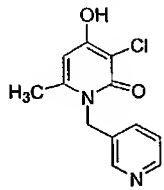
MS and ^{1}H-NMR for step 3 were consistent with the desired structure. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.48 (d, 2H, J= 5.2 Hz), 7.21 (m, 2H), 7.13 (d, 2H, J= 5.2 Hz), 6.98 (t, 2H, J= 9.0 Hz), 6.26 (s, 1H), 5.43 (s, 2H), 2.95 (m, 4H), 2.25 (s, 3H); ES-HRMS m/z 401.0682/403.0636 (M+H calculated for $C_{20}H_{19}N_2OFBr$ requires 401.0659/403.0641).

Example 441



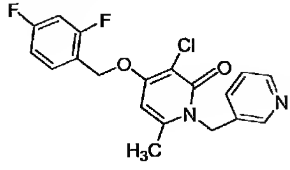
3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-chloro-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



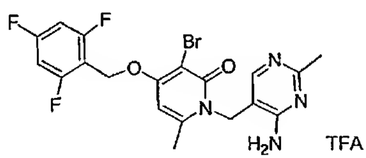
To a suspension of 4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (1.016 g, 4.7 mmol) in $MeCl_2$ (10 mL) was added NCS (1.21 g, 1.78 mmol). The reaction mixture stirred at room temperature for 24 hours under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh $MeCl_2$ and dried to afford a yellow solid (1.00 g, 85%) after drying. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.54 (m, 2H), 7.85 (d, 1H, J=1.6 Hz), 7.61 (m, 1H), 6.10 (s, 1H), 5.41 (s, 2H), 2.33 (s, 3H); ES-LRMS (M+H) m/z 251/253.

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



To a degassed cold solution of DMF (10 mL) and PPh_3 (resin, 2.2 g, 6.6 mmol) was added DEAD (1.038 mL, 6.6 mmol). The reaction mixture stirred at -10° C for 20 minutes under nitrogen. A solution of 3-chloro-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (1.00 g, 4.0 mmol) and 2,4-difluorobenzylalcohol (0.66 mL, 6.0 mmol) in DMF (10 mL) was added to the resin suspension. The reaction mixture stirred at -10° C for 30 minutes and then allowed to stir at room temperature for 1 hour. The resin was filtered and rinsed with fresh MeOH and the filtrate concentrated. The residue was dissolved in ethyl acetate and purified by flash column chromatography (5% methanol in ethyl acetate). The appropriate fractions were concentrated. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.45 (ddd, 2H, J= 1.6Hz, 1.6 Hz, 1.6 Hz), 7.61 (m, 2H), 7.41 (dd, 1H, J= 4.4 Hz, 4.8 Hz), 7.02 (m, 2H), 6.55 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H), 2.41 (s, 3H); ES-HRMS m/z 377.0882/379.0840 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Cl$ requires 377.0863/379.0840).

Example 442

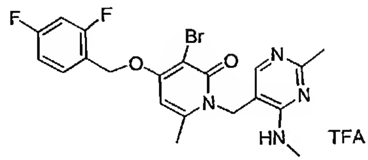


1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1H)-one trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 385, step 2 (0.142 g, 9%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.64 (s, 1H), 7.00 (m, 2H), 6.66 (s,

1H), 5.29 (s, 2H), 5.18 (s, 2H), 2.50 (s, 3H), 2.47 (s, 3H); ES-HRMS m/z 469.0488/471.0464 (M+H calculated for $C_{19}H_{17}N_4O_2F_3Br$ requires 469.0481/471.0463).

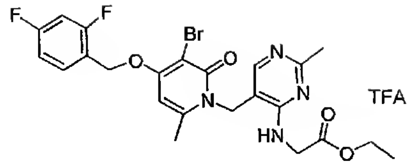
Example 443



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-methyl-4-(methylamino)pyrimidin-5-yl]methyl}pyridin-2(1H)-one trifluoroacetate

To a solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (0.15 g, 0.3 mmol) in DMF (3 mL) was added DBU (0.09 mL, 0.6 mmol). The solution was cooled in an ice bath and iodomethane (0.019 mL, 0.3 mmol) was added. The reaction mixture stirred at room temperature under nitrogen for 2 hours. The reaction was purified by reverse phase HPLC 10-90% CH3CN/water (30 minute gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 465 M+H) were combined and freeze dried to afford the desired product (0.036 g, 25%) as a white powder. ^1H NMR (CD_3OD, 400 MHz) δ 7.72 (s, 1H), 7.60 (m, 1H), 7.03 (m, 2H), 6.62 (s, 1H), 5.31 (s, 2H), 5.16 (s, 2H), 3.77 (s, 3H), 2.60 (s, 3H), 2.47 (s, 3H); ES-HRMS m/z 465.0717/467.0712 (M+H calculated for $C_{20}H_{20}N_4O_2F_2Br$ requires 465.0732/467.0714).

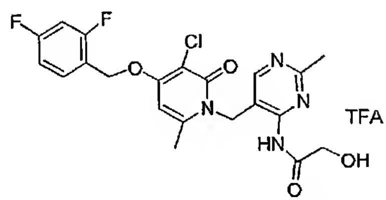
Example 444



ethyl N-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 442 with the exception that the reaction mixture had to be heated at oil bath temperature 70° C for 2 days (0.1384 g, 51 %). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.78 (s, 1H), 7.61 (m, 1H), 7.03 (m, 2H), 6.61 (s, 1H), 5.30 (s, 2H), 5.18 (s, 2H), 5.03 (s, 2H), 4.27 (q, 2H), 2.55 (s, 3H), 2.46 (s, 3H), 1.28 (t, 3H, J= 7.0 Hz); ES-HRMS m/z 537.0936/539.0932 (M+H calculated for $C_{23}H_{24}N_4O_4F_2Br$ requires 537.0943/539.0926).

Example 445

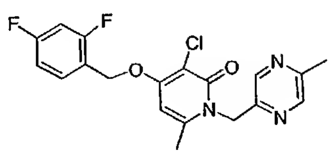


N-(5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)-2-hydroxyacetamide trifluoroacetate

To a chilled solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate (0.200 g, 0.38 mmol)

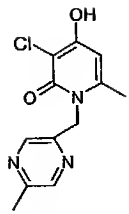
in DMF (20 mL) and a catalytic amount of DMAP was added triethylamine (0.064 mL, 0.38 mmol). The reaction stirred at -20° C and acetoxyacetyl chloride (0.082 mL, 0.76 mmol) was added. The reaction stirred cold for 15 minutes and then allowed to warm up to room temperature for 3 hours. The reaction was monitored by LR-ESMS m/z = 466. The reaction was incomlete after 3 hours. Added acetoxyacetyl chloride (0.05 mL, 0.466 mmol), and triethylamine (0.2 mL, 1.43 mmol) to the reaction mixture and continued to stir overnight at room temperature. The next morning the reaction heated at 65° C for 3 hours. The solvent was removed in vacuo and 1N LiOH (2.5 mL) was added to the residue. The reaction was heated at 60° C for 5 hours. The reaction was diluted with acetonitrile and water (1:1) and purified by reverse phase HPLC in 10-90% CH_3CN/water (30 minute gradient) at a flow rate of 50 mL/min. The appropriate fractions were freeze dried to afford the desired product (0.020 g, 9%). ^1H NMR (CD_3OD, 400 MHz) δ 8.04 (s, 1H), 7.6 (m, 1H), 7.02 (m, 1H), 6.59 (s, 1H), 5.30 (s, 2H), 5.24 (s, 2H), 4.26 (s, 1H), 2.60 (s, 3H), 2.43 (s, 3H); ES-HRMS m/z 465.1161 (M+H calculated for $C_{21}H_{20}N_4O_4F_2Cl$ requires 465.1136).

Example 446



3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

Step 1. Preparation of 3-chloro-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one



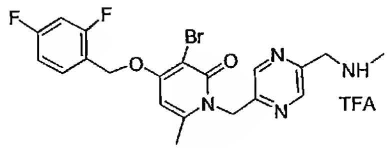
To a solution of 4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (1.00g, 4.3 mmol) in glacial acetic acid (10 mL) was added NCS (0.79 g, 5.94 mmol). The reaction mixture stirred at 60° C for 6 hours. The solvent was removed under reduced pressure and the resulting residue was triturated with ethyl acetate. The desired product was filtered and dried (0.80 g, 69%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47 (s, 1H), 8.42 (s, 1H), 6.08 (s, 1H), 5.36 (s, 2H), 2.50 (s, 3H), 2.43 (s, 3H); ES-HRMS m/z 266.0691 (M+H calculated for $C_{12}H_{13}N_3O_2Cl$ requires 266.0691).

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

To a solution of 3-chloro-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (2.48 g, 9.3 mmol) in DMA (7 mL)was added K_2CO_3 (1.54 g, 11.0 mmol) followed by 2,4-difluorobenzyl bromide (1.2 mL, 9.3 mmol). The reaction mixture stirred at room temperature under nitrogen for 1.5 hours. The solvent was distilled in vacuo. The resulting residue was diluted in dichloromethane and washed with water. The organic extracts were concentrated and the resulting residue was purified by flash column chromatography (ethyl acetate). The appropriate fractions were combined, and concentrated. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.49 (d, 1H, J=1.2 Hz), 8.40 (s, 1H), 7.59 (m, 1H), 7.04 (m, 2H), 6.54 (s, 1H),

5.41 (s, 2H), 5.28 (s, 2H), 2.54 (s, 3H), 2.40 (s, 3H); ES-HRMS m/z 392.1014 (M+H calculated for $C_{19}H_{17}N_3O_2ClF_2$ requires 392.0972).

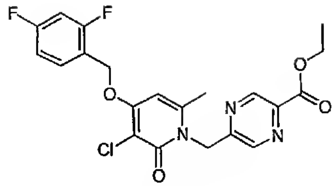
Example 447



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate

To a suspension of 3-bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.25 g, 0.53 mmol) in THF was added methylamine (1 mL, 2.1 mmol). The reaction was sealed and stirred at room temperature overnight. The reaction mixture was diluted in water:acetonitrile (1:1) and purified by reverse phase HPLC 10-90% CH_3CN/water (30 minute gradient) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to afford the desired product (0.22 g, 71%) as an amorphous solid. ^1H NMR (CD_3OD, 400 MHz) δ 8.73 (s, 1H), 8.55 (s, 1H), 7.6 (m, 2H), 7.02 (m, 1H), 6.54 (s, 1H), 5.47 (s, 2H), 5.29 (s, 2 H), 4.37 (s, 2 H), 2.78 (s, 3H), 2.56 (s, 3H). ES-HRMS m/z 465.0732/467.0709 (M+H calculated for $C_{20}H_{20}N_4O_2BrF_2$ requires 465.0732/467.0714).

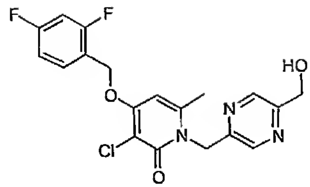
Example 448



Ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate

To a mixture of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.59 g, 2.07 mmol) and ethyl 5-(bromomethyl)pyrazine-2-carboxylate (0.62 g, 2.4 mmol) in THF (15 mL) was added NaH (0.06 g, 2.4 mmol). The reaction stirred at 60° C for 3.5 hours. The solvent was removed under reduced pressure and the residue was partitioned over dichloromethane and citric acid (5%). The organic extracts were washed with water and dried over Na_2SO_4 (anhydrous). The organic extracts were concentrated and the residue was purified by flash column chromatography (100 % ethyl acetate). The appropriate fractions were combined and concentrated under reduced pressure to remove solvent. ^1H NMR (CD_3OD, 400 MHz) δ 9.11 (d, 1H, J= 1.6 Hz), 8.77 (s, 1H), 7.52 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 4.49 (q, 2H), 2.52 (s, 3H), 1.39 (t, 3H, J= 7.2 Hz); ES-HRMS m/z 450.1045 (M+H calculated for $C_{21}H_{19}N_3O_4ClF_2$ requires 450.01027).

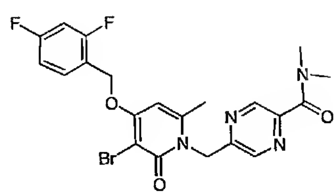
Example 449



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a suspension of ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (4.0 g, 8.9 mmol) in THF:t-butanol (1:1) (10 mL) was added $NaBH_4$ (0.46 g, 12.4 mmol). The reaction stirred at room temperature under argon overnight. The reaction mixture was quenched with acetic acid (2 mL) and the solvent was removed in vacuo. The residue was triturated with water and filtered. The solid was washed with fresh water followed by ethanol. The solid was purified by flash column chromatography (100% ethyl acetate). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired compound (1.58 g, 44%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.59 (s, 1H), 8.56 (s, 1H), 7.52 (m, 1H), 7.01 (m, 2H), 6.55 (m, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 4.71 (2H), 2.54 (s, 3H); ES-HRMS m/z 408.0940 (M+H calculated for $C_{19}H_{17}N_3O_3ClF_2$ requires 408.0921).

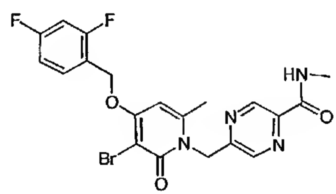
Example 450



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylpyrazine-2-carboxamide

To a cold solution of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0.175 g, 0.37 mmol) in DMF (5 mL, -10° C) was added IBCF (0.046 mL, 0.35 mmol) followed by NMM (0.041 mL 0.37 mmol). The reaction was activated for 20 minutes at -15° C after which dimethylamine (0.375 mL, 0.74 mmol) was added. The reaction stirred at -10° C to room temperature for 45 minutes. The solvent was removed in vacuo and the residue was purified by reverse phase HPLC 10-90% CH_3CN/water (30 minute gradient) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to afford the desired product (0.140g, 75%) as a white solid. ^1H NMR (CD_3OD, 400 MHz) δ 8.68 (s, 1H), 8.67 (s, 1H), 7.52 (m, 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.50 (s, 2H), 5.30 (s, 2H), 3.11 (s, 3 H), 3.07 (s, 3H), 2.55 (s, 3H); ES-HRMS m/z 493.0680/495.0657 (M+H calculated for $C_{21}H_{20}N_4O_3BrF_2$ requires 493.0680/495.0657).

Example 451

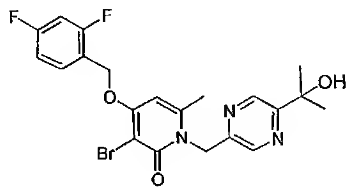


5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-methylpyrazine-2-carboxamide

The title compound was prepared essentially as in Ex. 450, substituting dimethylamine with methylamine. ^1H NMR (CD_3OD, 400

MHz) δ 9.07 (s, 1H), 8.68 (s, 1H), 7.54 (m, 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.52 (s, 2H), 5.30 (s, 2H), 2.94 (s, 3H), 2.54 (s, 3H); ES-HRMS m/z 479.0542/481.0518 (M+H calculated for $C_{20}H_{18}N_4O_3BrF_2$ requires 479.0525, 481.0507).

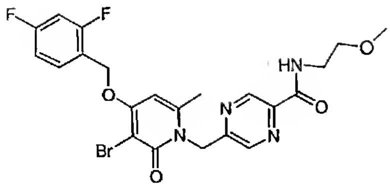
Example 452



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a cold flask of MeMgBr (1.59 mL, 1.0 mmol) was added a suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (0.5 g, 1.0 mmol) in THF (20 mL). The reaction stirred at 0° C for 1.5 hours and then at room temperature overnight. The reaction was quenched with cold citric acid (25 mL, 5%) and extracted with ethyl acetate (2 X 100 mL). The organic extracts were washed with fresh water. The organic extracts were concentrated and purified by reverse phase HPLC 10-90% CH_3CN/water (30 minute gradient) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to afford the desired product (29.9 mg, 6%). ^1H NMR (CD_3OD, 400 MHz) δ 8.76 (d, 1H, J= 1.6 Hz), 8.54 (d, 1H, J= 1.2 Hz), 7.52 (m, 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.55 (s, 3H), 1.52 (s, 6H); ES-HRMS m/z 480.0745/482.0722 (M+H calculated for $C_{21}H_{21}N_3O_3BrF_2$ requires 480.0729/482.0711).

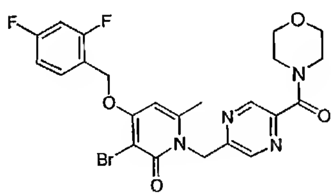
Example 453



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-methoxyethyl)pyrazine-2-carboxamide

The title compound was prepared essentially as in Ex. 450, substituting dimethylamine with 2-methoxyethylamine. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.08 (d, 1H, J= 1.2 Hz), 8.70 (d, 1H, J= 1.2 Hz), 7.61 (m, 1H), 7.04 (m, 2H), 6.54 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 3.56 (m , 4H), 3.30 (s, 3H), 2.54 (s, 3H); ES-HRMS m/z 523.0822/525.0810 (M+H calculated for $C_{22}H_{22}N_4O_4BrF_2$ requires 523.0787/525.0770).

Example 454

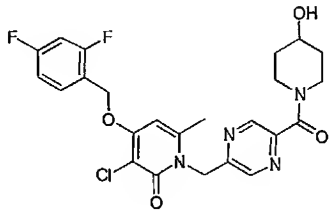


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[5-(morpholin-4-ylcarbonyl)pyrazin-2-yl]methyl}pyridin-2(1H)-one

The title compound was prepared essentially as in Ex. 450, substituting dimethylamine with morpholine. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.77 (d, 1H, J= 1.6 Hz), 8.67 (s, 1H), 7.54 (m, 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.50 (s, 2H), 5.30 (s,

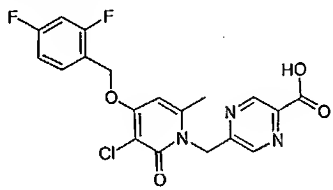
2H), 3.75 (s, 4H), 3.59 (dd, 4H, J= 5.6 Hz, 5.2 Hz), 2.55 (s, 3H); ES-HRMS m/z 535.0816/537.0817 (M+H calculated for $C_{23}H_{22}N_4O_4BrF_2$ requires 535.0787/537.0770).

Example 455



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one

Step 1. Preparation of 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid



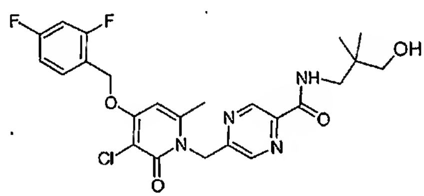
A mixture of ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (1.03g, 2.3 mmol) in 1N NaOH (3.4 ml, 3.45 mmol, EtOH/water 1:1 v/v) stirred at room temperature for 2 hours. The reaction mixture was quenched with 5% citric acid and filtered. The solid was washed with water and dried to afford the desired product (1.011 g, 100%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.02 (s, 1H), 8.60 (s, 1H), 7.60 (m, 1H), 7.04 (m, 2H), 6.55 (s, 1H), 5.50

(s, 2H), 5.30 (s, 2H), 2.52 (s, 3H); ES-HRMS m/z 422.0732 (M+H calculated for $C_{19}H_{15}N_3O_4ClF_2$ requires 422.0714).

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 453 (0.1396 g, 47%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.67 (s, 2H), 7.59 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.49 (s, 2H), 5.30 (s, 2H), 4.16 (m, 1H), 3.89 (septet, 1H), 3.72 (m, 1H), 3.38 (m, 2H), 2.56 (s, 3H), 1.93 (m, 1H), 1.83 (m, 1H), 1.45 (m, 2H); ES-HRMS m/z 505.1485 (M+H calculated for $C_{24}H_{24}N_4O_4ClF_2$ requires 505.1449).

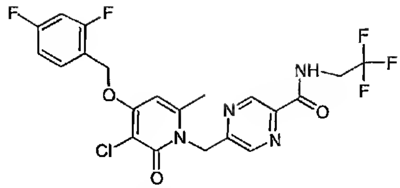
Example 456



5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(3-hydroxy-2,2-dimethylpropyl)pyrazine-2-carboxamide

The title compound was prepared by a procedure similar to the one described for Example 455 (0.215 g, 71%). ^{1}H NMR (CD_3OD, 400 MHz) δ 9.08 (d, 1H, J= 1.2 Hz), 8.71 (d, 1H, J= 1.6 Hz), 7.58 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.52 (s, 1H), 5.30 (s, 1H), 3.31 (s, 4H), 2.55 (s, 3H), 0.912 (s, 6H); ES-HRMS m/z 507.1630 (M+H calculated for $C_{24}H_{26}N_4O_4ClF_2$ requires 507.1605).

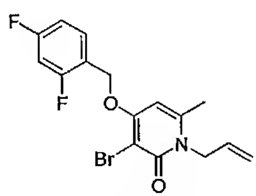
Example 457



5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide

The title compound was prepared by a procedure similar to the one described for Example 455 except no purification was required, only a $NaHCO_3$/ethyl acetate extraction was needed (0.2176 g, 73%). ^1H NMR (CD_3OD, 400 MHz) δ 9.11 (d, 1H, J= 1.6Hz), 8.73 (d, 1H, J= 1.3 Hz), 7.59 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 4.01 (q, 2H), 2.54 (s, 3H); ES-HRMS m/z 503.0930 (M+H calculated for $C_{21}H_{17}N_4O_3ClF_5$ requires 503.0904).

Example 458



1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: 1-allyl-4-hydroxy-6-methylpyridin-2(1H)-one. 4-hydroxy-6-methyl-2-pyrone (2g, 16 mmol) was stirred in water (25 mL). Allylamine (1.2 ml, 16mmol) was added to the

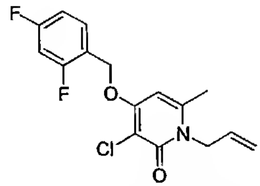
reaction. The reaction was then heated to 100 °C at which point the reaction became homogeneous. The reaction was stirred at 100 °C for 2h. The reaction was then allowed to cool to rt after which a white precipitate formed. The precipitate was isolated by suction filtration. After additional washing with water, 1.8g (69%) of an off-white solid was obtained.

Step 2: 1-allyl-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one. To a stirred solution of the above pyrone(4.0g, 24 mmol) in DMF(75ml) was added Cs_2CO_3 (7.8g, 24mmol) followed by addition of 2,4-diflurorbenzyl bromide(3.4 mmol, 26.4 mmol). The resulting mixture was stirred at rt for 2h. Additional Cs_2CO_3 (1g) and bromide (1 ml) was added and the reaction was stirred for an additional 2h. The Cs_2CO_3 was removed by suction filtration. The DMF was removed under vacuum and the crude material was purified by flash chromatography. Elution with ethyl acetate-hexanes (2:1 to 1:1) afforded 1.5 g (21%) of the desired compound.

Step 3: 1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one. To a stirred suspension of the above pyridinone (1g, 3.4 mmol) in CH_3CN (10 ml) was added n-bromosuccinimide (670 mg, 3.8 mmol). The reaction mixture was stirred, at rt, for 3h. The product was obtained by filtration of the reaction mixture and washing of the solid with diethyl ether. ^{1}H-NMR ($DMSO_{d6}$/400 MHz) δ 7.62 (app q, J = 8.8 hz, 1H), 7.31 (ddd, J = 12.0, 9.6, 2.8 hz, 1H); 7.15 (app dtd, J = 8.4, 2.4, 0.8 Hz, 1H); 6.50 (s, 1H); 5.87 (ddt, J = 12.4, 10.4, 5.6 Hz, 1H), 5.30 (s, 2H), 5.10 (dd, J = 10, 1.6 Hz, 1H), 4.87 (dd, J = 17.6, 1.6 Hz, 1H), 4.64 (m, 2H), 2.34 (s, 3H); 19F-NMR ($DMSO_{d6}$/282.2 MHz) −109.68 (quin, J = 1H), -

113.66(quar, J = 1H); HRMS m/z 370.0255 (M + H calcd for $C_{16}H_{15}BrF_2NO_2$ = 370.0246).

Example 459



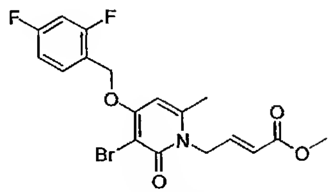
1-allyl-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: 1-allyl-3-chloro-4-hydroxy-6-methylpyridin-2(1H)-one. To a stirred solution of 1-allyl-4-hydroxy-6-methylpyridin-2(1H)-one (500 mg, 3.0 mmol) in CH_3CN(10 ml), at rt, was added sequentially n-bromosuccinimide (440 mg, 3.3 mmol) and dichloroacetic acid (546 µl, 6.62 mmol). The resulting mixture was stirred for 2h. The heterogeneous mixture was filtered and the solid was washed with additional CH_3CN to give 350 mg (59%) of the desired product as a tan solid. ^{1}H-NMR ($DMSO_{d6}$/300 MHz) δ 11.16 (s, 1H), 5.98-5.86 (m, 2H), 5.12 (dd, J = 10.5, 1.5 Hz, 1H), 4.89 (dd, J = 17.1, 1.5 Hz, 1H), 4.63-4.61 (m, 2H), 2.29 (s, 3H). ES-HRMS m/z 200.050 (M + H calcd for $C_9H_{11}ClNO_2$ = 200.0470)

Step 2: 1-allyl-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one. The title compound was prepared by the procedure outline in the synthesis of Example 458, step 3. ^{1}H-NMR ($DMSO_{d6}$/300 MHz) δ 7.67 (app q, J = 8.4 hz, 1H), 7.36 (app dt, J = 10.2, 2.7 hz, 1H); 7.15 (m, 1H); 6.58 (s, 1H); 5.93 (ddt, J = 15.3, 9.6, 4.8 Hz, 1H), 5.30 (s, 2H) 5.15 (dd, J = 10.2, 1.2 Hz, 1H), 4.92 (dd, J = 17.4, 1.2 Hz, 1H), 4.69-

4.67 (m, 2H), 2.41 (s, 3H). ES-HRMS m/z 326.0760 (M + H calcd for $C_{16}H_{15}ClF_2NO_2$ = 326.0790).

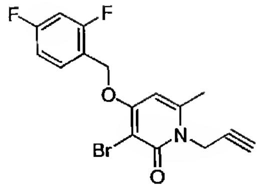
Example 460



Methyl (2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]but-2-enoate

To a stirred suspension of NaH (277 mg, 11 mmol) in anhydrous THF (30 ml), which was cooled to 0°C, was slowly added 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (3.3g, 10 mmol). The resulting slurry was stirred for 15 min, after which methyl 4-bromocrotonate (1.4 ml, 12 mmol) was added to the reaction. The ice bath was removed and the reaction was heated to reflux for 16h. The reaction was quenched by the addition of 1N NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5x). The organics were combined, dried, and concentrated in vacuo. The crude yellowish material was then triturated with Et_2O to give, after filtration and drying, 1.8g (43%) of a white solid. ^{1}H-NMR ($DMSO_{d6}$/300 MHz) δ 7.65 (app q, J = 8.7 hz, 1H), 7.36 (app dt, J = 12.0, 3.0 hz, 1H); 7.17 (dt, J = 8.4, 1.8 Hz, 1H); 6.94 (dt, J = 15.9, 4.5 Hz, 1H); 6.57 (s, 1H), 5.52 (d, J = 15.9 Hz, 1H), 5.29 (s, 2H), 4.84 (m, 2H), 3.63 (s, 3H), 2.33 (s, 3H). ES-HRMS m/z 428.0301 (M + H calcd for $C_{18}H_{17}BrF_2NO_4$ = 428.0310).

Example 461

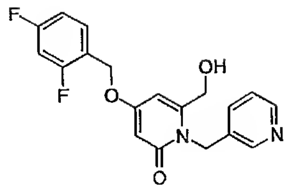


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-ynylpyridin-2(1H)-one.

Step1: 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-ynylpyridin-2(1H)-one. The title compound was prepared by alkylation of 4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2.5g, 10 mmol) with propargyl bromide (1.3 ml, 11.0 mmol) as described above to give 1.3g (44%) of the desired product. ^{1}H- NMR (DMSO$_{d6}$/300 MHz) δ 7.60 (app q, J = 8.4 hz, 1H), 7.35-7.27 (m, 1H); 7.16-7.10 (m, 1H); 5.94 (d, J = 2.1 Hz, 1H), 5.88 (d, J = 3.0 Hz, 1H), 5.03 (s, 2H), 4.76 (d, J = 2.4, Hz, 2H), 3,31 (s, 3H), 3.24 (t, J = 2.4 Hz, 1H), 2.39 (s, 3H); ES-HRMS m/z 290.0994 (M + H calcd for $C_{16}H_{14}F_2NO_2$ = 290.0993).

Step 2: Bromination of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-ynylpyridin-2(1H)-one (500 mg, 1.67 mmol) with NBS (300 mg, 1.67 mmol) was carried out in the manner described above to give 350 mg (57%) of the desired compound. ^{1}H-NMR (DMSO$_{d6}$/300 MHz) δ 7.67 (app q, J = 9.0 hz, 1H), 7.36 (app dt, J = 10.5, 2.4 hz, 1H); 7.23-7.16 (m, 1H); 6.60 (s, 1H), 5.29 (s, 2H), 4.90 (d, J = 2.4, Hz, 1H), 3.35 (s, 3H), 3.32 (s, 1H), 2.53 (s, 3H); ES-HRMS m/z 368.0107 (M + H calcd for $C_{16}H_{13}BrF_2NO_2$ = 368.0098).

Example 462



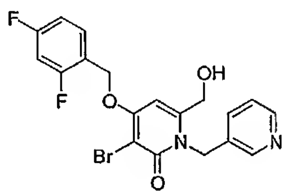
4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one.

Step1: To a suspension of (4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one) (710 mg, 2 mmol) in dioxane (10 mL) was added selenium dioxide (1.1g 10 mmol). The resulting mixture was heated to 160 °C in a 125 mL sealed tube for 1h. The reaction was filtered through a fritted funnel. The filtrate was washed with (10:1) CH_2Cl_2-MeOH. The organics were combined and concentrated in vacuo. The crude material was purified by flash chromatography. Elution with (50:50 → 0:100)hexanes yielded 450 mg (63%) of the aldehyde. ^{1}H-NMR ($DMSO_{d6}$/400 MHz). δ 9.48 (s, 1H, CHO).

Step 2: The aldehyde (350 mg, 1 mmol) was dissolved in MeOH (4 mL) and cooled to 0 °C . To this mixture was added $NaBH_4$ (28 mg, 1 mmol) in one portion. After 30 min, additional NaBH4 (20 mg) was added to the reaction. The MeOH was then removed under vacuum. The residue was diluted with 1N NH_4Cl and then extracted with CH_2Cl_2(4X). The organics were combined, dried, and concentrated in vacuo. The yellowish crude product was then taken up in (1:1) CH_2Cl_2-Et_2O. After sitting for a period of time a white precipitate resulted. Filtration and washing with additional Et_2O yielded, after drying, 250 mg (55%) of the desired alcohol. ^{1}H-NMR ($DMSO_{d6}$/400 MHz). δ 8.42 (dd, J = 4.4,

1.6 Hz, 1H) 8.37 (d, J = 1.6 Hz, 1H), 7.61 (app q, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.32-7.27(M, 2H), 7.12 (dt, J = 8.4, 1.6 Hz, 1H), 6.07 (d, J = 2.8 Hz, 1H), 5.99 (d, J = 12.8 Hz, 1H), 5.63 (br s, 1H), 5.18 (s, 2H), 5.09 (s, 2H), 4.29 (s, 2H). LC/MS, t_r = 1.19 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 359.1 (M+H)

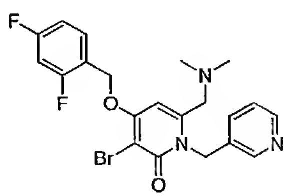
Example 463



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one.

The title compound was prepared by bromination of as described above to give a 60% yield. ^{1}H-NMR ($DMSO_{d6}$/300 MHz). δ 7.93 (d, J = 7.8 Hz, 1H), 7.73-7.65 (m, 3H), 7.38 (dt, J = 10.2, 2.4 Hz, 1H), 7.21 (app t, J = 8.7 Hz, 2H), 6.74 (s, 1H), 5.38.-5.36 (m, 4H), 4.50 (s, 2H); ES-HRMS m/z 437.0311 (M + H cacld for $C_{19}H_{16}BrF_2N_2O_2$ = 437.0313).

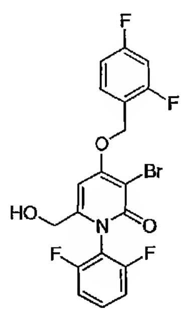
Example 464



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-[(dimethylamino)methyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one.

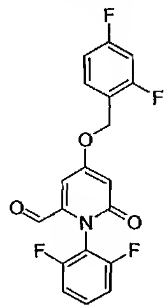
The title compound was prepared in a similar manner to the procedure outlined below for 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)-methyl]pyridin-2(1H)-one using the aldehyde (300 mg, 0.85 mmol) described above and 2.0 N THF solution of dimethylamine (500 μL, 1 mmol) to give 110 mg (34%) of a colorless oil. The oil was then dissolved in MeOH (1 mL) and stirred with fumaric acid (25 mg) for 1h. The resulting precipitate was filtered, washed with diethyl ether, and dried to give the pure product as it's fumurate salt. ^{1}H-NMR ($DMSO_{d6}$/400 MHz). δ 8.43-8.41 (m, 1H), 8.35 (s, 1H), 7.67-7.61 (m, 1H), 7.44-7.40 (m, 1H), 7.35-7.29 (m, 2H), 7.17-7.12 (m, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 5.41 (s, 2H), 5.32 (s, 2H), 3.13 (s, 2H), 2.12 (s, 6H). LC/MS, t_r = 1.55 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 464 (M+H).

Example 465



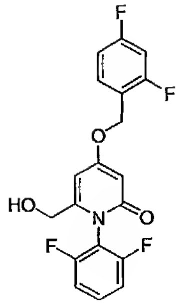
3-bromo-4- [(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

Step1: 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde.



In a 300 ml high-pressure glass reaction vessel (16.3 g, 45 mmol) was dissolved in 1,4-dioxane (90 mL). The reaction vessel was sealed and immersed in a preheated oil bath at 170 ° C. The reaction was heated at 170° C (165 -170 °C) for 1.5 hours and then cooled to room temperature. The reaction was worked up by filtering the reaction mixture through a plug of celite and silica gel. The plug was then washed with 500 ml of methanol-CH_2Cl_2 mixture (1:5). The filtrate was evaporated to give 14.2 g of the desired crude aldehyde.

Step 2: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one.

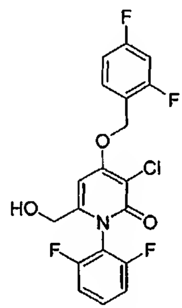


In a 500 ml three neck round bottom flask equipped with a stir bar of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (14.2 g, 37.7 mmol) was dissolved in methanol (200 mL). The reaction mixture was cooled to 0 °C and to this was added sodium borohydride (2.13g, 56.30 mmol) in a slow portion-wise fashion. The reaction was stirred at 0 °C for 2 hour. Excess amount of sodium borohydride was added to drive the reaction to completion. After stirring for approximately 2.5 hours, the reaction was allowed to warm to room temperature and then concentrated to dryness. The residue was taken up in ethyl acetate (100 mL) and washed with dilute HCl (pH of aqueous layer was approximately 4). Organic extracts were washed with brine (1X 50 ml), dried over $MgSO_4$, and concentrated in vacuo. The crude product was recrystallized from ethyl acetate and hexane to yield 7.56 g (44% yield-starting from step 1) of the desired alcohol.

Step 3: Preparation of the title compound.
In a 100 ml round bottom flask of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one (2.49 g, 6.56 mmol), from step 2, was dissolved in acetonitrile (35 mL). The reaction mixture was cooled to 0 °C in ice bath for 10 min. and then charged with N-bomosuccinamide (1.17g, 6.6 mmol) . The mixture was allowed

to stir, at 0 °C, under nitrogen atmosphere for 2 hours. The reaction was the worked up by removing the acetonitrile under vacuum. The resulting residue was then filtered, with washing from a small amount of acetonitrile, to give a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.695 - 7.588 (m, 2H), 7.368-7.314 (m, 3H), 7.175 (dt, J = 8.5, 2.5, Hz, 1H), 6.760 (s, 1H), 5.712 (t, J = 5.674 Hz, 1H), 5.384 (s, 2H), 4.004-3.990 (m, 2H); ES-HRMS m/z 458.0013 (M+H-calcd for $C_{19}H_{13}BrF_4NO_3$, requires 458.0013).

Example 466

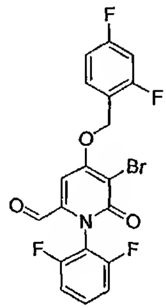


3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

The title compound was prepared by taking 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one (1.5g, 3.9 mmol) in acetonitrile (15 mL) and adding to that N-chlorosuccinimide (580 mg, 4.3 mmol). The reaction was stirred at rt for 3h afterwhich a small amount of additional N-chlorosuccinimide (50 mg, 0.4 mmol) was added to the reaction. Stirring was continued for 1h. The reaction mixture was filtered through a fritted funnel to obtain the crude material. ^1H NMR (400 MHz, DMSO-d_6) δ 7.69 - 7.61 (m, 2H), 7.37-7.31 (m, 3H), 7.17 (dt, J

= 8.8, 2.0 Hz, 1H), 6.80 (s, 1H), 5.70 (t, J = 6.0 Hz, 1H), 5.38 (s, 2H), 4.01 (d, J = 6.0 Hz, 2H); ES-HRMS m/z 414.0515 (M+H calcd for $C_{19}H_{13}ClF_4NO_3$, requires 414.0520).

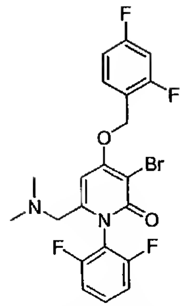
Example 467



5-bromo-4-[(2,4-difluorobenzyl)oxy]
-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde

Preparation of the title compound. In a 50 ml one neck round bottom flask 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0.36 g, 0.95 mmol) was dissolved in acetonitrile (5 mL). The reaction mixture was cooled to 0 °C in ice bath and charged with N-bromosuccinamide (0.17 g, 0.95 mmol). The mixture was allowed to stir at 0 °C for 2 hours under nitrogen atmosphere After 2 hours, the solvent was evaporated under vacuum. ^1H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.73 - 7.67 (m, 2H), 7.62-7.54 (m, 1H), 7.35 (dt, J = 10.40, 2.56 Hz, 1H), 7.27 (t, J=8.35 Hz, 2H), 7.19 (dt, J =8.60, 2.44 Hz, 1H), 5.72 (s, 1H), 5.50 (s, 2H); ES-MS m/z 455.9836 (M+H calcd for $C_{19}H_{11}BrF_4NO_3$, requires 455.9859).

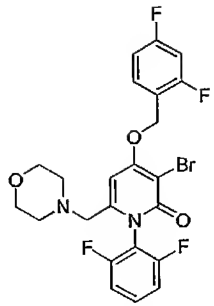
Example 468



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1H)-one

In a 50 ml round bottom flask 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0.456 gm, 1.0 mmol) was stirred in dichloromethane (5 mL). To this mixture was added a 2M THF solution of dimethyl amine (1.25ml, 2.5 mmol). The mixture was allowed to stir under nitrogen atmosphere and at room temperature for 2 hours. To this mixture was then added triacetoxy sodium borohydride (0.37 g, 1.75 mmol) followed by two to three drops of acetic acid. The mixture was then stirred at rt overnight. The solvents were then removed by evaporation and the residue was taken up in ethyl acetate (30 ml) and washed with aqueous sodium bicarbonate and brine. The organics were then combined, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography using a solvent gradient of (3:1) ethyl acetate-hexane to (0:100) ethyl acetate to give 0.14 g (30 % yield) of the desired product. ^1H NMR (300 MHz, DMSO-d_6) δ 7.73-7.58 (m, 2H), 7.42-7.30 (m, 3H), 7.22 (dt, J=8.73, 2.60 Hz, 1H), 6.81 (s, 1H), 5.44 (s, 2H), 3.04 (s, 2H), 1.96 (s, 6H); ES-MS m/z 485.0 (M+H). ES-HRMS m/z 485.0457 (M+H calcd for $C_{21}H_{18}BrF_4N2O_2$, requires 485.0489).

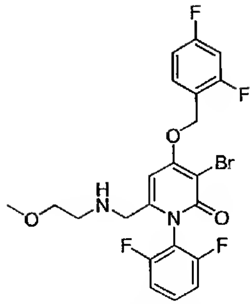
Example 469



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(morpholin-4-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by reacting 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0.456 g, 1mmol) with morpholine (0.13 ml, 1.5 mmol) and triacetoxy sodium borohydride (0.42 g, 2.0 mmol) in dichloromethane (7 mL) by using a similar procedure to the one described for Example 468. The crude product was purified by flash column chromatography. Elution with (50:50 → 0:100) hexanes-ethyl acetate to give 0.15 g (29% yield) of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75- 7.57 (m, 2H), 7.43-7.31 (m, 3H), 7.20 (dt, J=8.64, 2.48 Hz, 2H), 6.85 (s, 1H), 5.44 (s, 2H), 3.37 (app t, J=4.37 Hz, 4H), 3.13 (s,2H), 2.08 (t, J=4.19 Hz, 4H); ES-HRMS m/z 527.0600 (M+H calcd for $C_{23}H_{20}BrF_4N_2O_3$ requires 527.0594).

Example 470

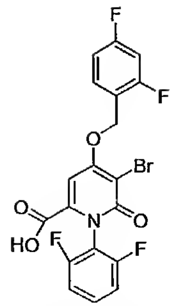


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-{[(2-methoxyethyl)amino]methyl}pyridin-2(1H)-one

The title compound was prepared by reacting 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde -(0.319 g, 0.7 mmol) with 2-methoxy ethylamine (0.086 ml, 1.0 mmol) and triacetoxy sodium borohydride (0.42 g, 2.0 mmol) in dichloromethane (4 mL) by using a procedure, similar to the one described for Example 468. The crude product was purified by flash column chromatography. Elution with (50:50 → 0:100) hexanes-ethyl acetate to give 0.13 g of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (q, J=6.89 Hz, 1H), 7.41 - 7.33 (m, 1H), 7.19 (s, 1H), 6.99 (t, J = 7.90 Hz, 2H), 6.90 (dt, J=7.90, 2.78, Hz, 1H), 6.80 (dt, J = 10.60, 2.34 Hz, 1H), 6.51 (s,1H), 5.24 (s,2H), 3.33 (t, J=4.69 Hz,1H), 3.30 (s, 3H), 2.57(t, J= 4.86 Hz, 2H), 1.53 (s,2H); ES-HRMS m/z 515.0548 (M+H calcd for $C_{22}H_{20}BrF_4N_2O_3$, requires 515.0594).

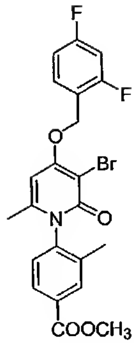
Example 471



5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid

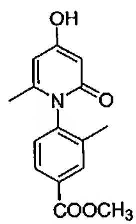
In a 100 ml round bottom flask, 3-bromo-4- [(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6 (hydroxymethyl)pyridin-2(1H)-one (1.70 g, 3.7 mmol) was dissolved in acetone (10 mL) and cooled to 0 ° C in ice bath. To the reaction was added 1M acetone solution of Jones (5 ml, excess amount). Additional Jones reagent was added over time (approximately 6 hours) until the reaction was complete. The reaction was then concentrated down to dryness. The residue was then taken up in ethyl acetate (10 mL) and washed with brine. The dark yellow to brown colored crude product was purified by dissolving in 1N aqueous NaOH. The remaining organic impurities were removed by extracting with diethyl ether. The organic layers were discarded and the aqueous layer was acidified with dilute HCl (til $_{p}$H app 1) to precipitate the pure acid which was then filtered and triturated with ether to obtain 1.17 g (65%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (q, J= 9.41 Hz, 1H), 7.57- 7.50 (m, 1H), 7.34 (dt, J= 10.11, 2.78 Hz, 1H), 7.28- 7.23 (m, 3H), 7.18 (dt, 8.90, 2.42 Hz, 1H), 5.47 (s, 2H). ES-HRMS m/z 471.9814 (M+H calcd for $C_{19}H_{11}BrF_4NO_4$, requires 471.9808)

Example 472



Methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-methylbenzoate

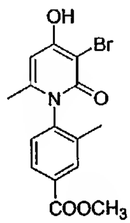
Step1: Preparation of methyl 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate .



In a 50 ml one neck round bottom flask equipped with a stir bar, Dean Stark trap, and condenser 4-amino-2-methyl-methylbenzoate (1.19g, 11.63 mmol) and 4-hydroxy-6-methyl-2H-pyran-2-one (1.611g, 12.78 mmol) were mixed together and dissolved in 1,2-dichlorobenzene (5 mL). The mixture was vigorously stirred and then placed in a preheated oil bath at 165 0 °C. The reaction was maintained at 165 0 °C for 1.5 hour and cooled to room temperature. The reaction was worked up by diluting with toluene (10 mL) and then stirring at room temperature for 2 hours. A light brown precipitate resulted. The crude product was isolated by filtration and then

triturated with ether. ^1H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.93 (s,1H), 7.85 (dd, 8.46 Hz, 1H), 7.26 (d , J= 8.12 Hz, 1H), 5.91 (d, J= 2.32 Hz, 1H), 5.54 (d, J=2.32 Hz, 1H), 3.84 (s, 3H), 1.99 (s, 3H), 1.73 (s,3H). ES-HRMS m/z 272.0880 (M-H calcd for $C_{15}H_{14}NO_4$, requires 272.1001).

Step 3: Preparation of Methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1 (2H)-yl)-3-methylbenzoate

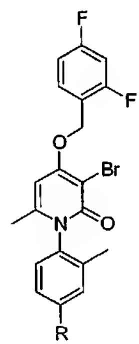


Methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate was prepared by reacting - methyl 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate with N-bomosuccinamide in acetonitrile by following a procedure, similar to the one described in Example 465- step 3. ^1H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.87 (dd, J = 7.76, 2.02 Hz, 1H), 7.31 (d, J=8.54, 1H), 6.09 (s,1H), 3.85 (s, 3H), 1.99 (s,3H), 1.74 (s, 1H). ES-HRMS m/z 352.0195 (M+H calcd for $C_{15}H_{14}BrNO_4$, requires 352.0185)

Step 4: The title compound was prepared by taking methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate (0.92 g, 2.61 mmol) and dissolving in dry DMF (5 mL). Potassium carbonate (0.432 g, 3.13 mmol) and 2,4 Difluuorobenzyl bromide (0.335 ml, 2.61 mmol) were then added. The mixture was allowed to stir at room temperature for 2 hours.

The reaction was then worked up by pouring it into 100 ml of ice-water which resulted in a precipitate forming which was isolated by filtering through a fritted funnel. The crude product was washed with ether and dried in vacuum to give 0.85 g (76.20%) of pure product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 1.6 Hz, 1H), 7.88 (dd, J =8.04, 2.0 Hz, 1H), 7.69 (q, J = 8.6 Hz, 1H), 7.36-7.30 (m, 2H), 7.17 (dt, J = 8.7, 2.3 Hz, 1H), 6.71 (s,1H), 5.32 (s,2H), 3.86 (s,3H), 2.00 (s,3H), 1.86 (s, 3H). ES-HRMS m/z 478.0459 (M+H calcd for $C_{22}H_{19}BrF_2NO_4$ requires 478.0466).

Examples 473-476



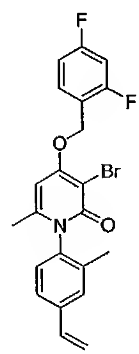
The compounds of Examples 473-476 are prepared by derivitazion of the compounds of Example 472.

Compound No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 473	$-CO_2H$	$C_{21}H_{16}BrF_2NO_4$	464.0310	464.0324
Ex. 474	$-CH_2OH$	$C_{21}H_{18}BrF_2NO_3$	450.0500	450.0517
Ex. 475	$C(O)NH(CH_2)_2OCH_3$	$C_{24}H_{22}BrF_2N_2O_4$	521.0888	521.0865
Ex. 476	$C(O)NHCH_3$	$C_{22}H_{20}BrF_2N_2O_3$	477.0626	477.0609

NMR characterization of compounds of Examples 473-476

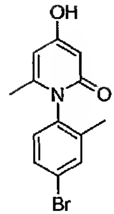
Ex.No.	NMR Data
473	^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.95 (d, J = 1.70 Hz, 1H), 7.86 (dd, J=7.88, 1.91 Hz, 1H), 7.67 (dq, J = 8.47, 1.89 Hz, 1H), 7.36-7.30 (m, 2H), 7.17 (dt, J =8.54, 2.48 Hz, 1H), 6.71 (s,1H), 5.32 (s,2H), 1.99 (s, 3H), 1.87 (s, 3H)
474	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (q, J =8.5 Hz,1H), 7.34 (dd, J =10.04, 2.77 Hz, 1H), 7.32 (s, 1H), 7.24 (dd, J = 8.39,1.47 Hz, 1H), 7.17 (dt, J = 8.84,2.6 Hz, 1H), 7.08(d, J = 7.94 Hz, 1 H), 6.66 (s,1H), 5.30 (s, 2H), 5.25 (t, J = 6.01 Hz, 1H), 4.5 (d, J =6.68 Hz, 2H), 1.91 (s, 3H), 1.86 (s,3H)
475	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (app t, J =5.4 Hz,1H), 7.84 (s,1H), 7.76 (dd, J= 8.06, 1.63 Hz, 1H), 7.68 (dq, J= 8.77, 2.04 Hz, 1H), 7.33 (dt, J=9.76, 2.03 Hz, 1H), 7.27 (d, J=8.34 Hz,1H), 7.17 (ddt, J=8.51, 2.63, 0.91 Hz, 1H), 6.70 (s, 1H), 5.31 (s,2H), 4.50 (t, J=5.6 Hz , 1H), 3.47-3.36 (m, 4H), 3.24 (s, 3H), 1.97 (s,3H), 1.87 (s,3H)
476	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50-8.49 (m, 1H), 7.82 (s, 1H), 7.74 (dd, J=8.22, 1.79 Hz, 1H), 7.69 (q, J= 6.75 Hz, 1H), 7.33 (dt, J= 9.88, 2.57 Hz, 1H), 7.26(d, J=8.52 Hz, 1H), 7.17(dt, J= 8.93, 2.16 Hz, 1H), 6.69 (s, 1H), 5.31 (s, 2H), 2.77 (d, J= 4.58 Hz, 3H), 1.97 (s, 3H), 1.86 (s, 3H)

Example 477



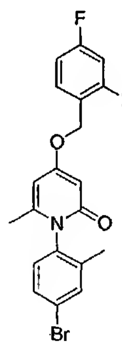
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one

Step 1- Preparation of -1-(4-bromo-2-methylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



The title compound was prepared in a similar manner to the procedure outlined above for 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.59 (d, J= 2.84 Hz, 1H), 7.45 (dd, J= 8.39, 2.44 Hz, 1H), 7.06 (d, J= 7.44, 1H), 5.89 (d, J=2.73 Hz, 1H), 5.53(d, J=2.30, 1H), 1.91 (s, 3H), 1.75 (s, 3H). ES-HRMS m/z 294.0127 (M+H calcd for $C_{13}H_{13}BrNO_3$, requires 294.0130).

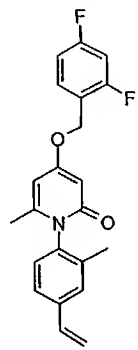
Step 2- Preparation of - 1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



1-(4-bromo-2-methylphenyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (7.35 g, 25.0 mmol) was dissolved in DMF (15 mL) and stirred with potassium carbonate (4.14 g, 30.0 mmol) and 2,4 difluorobenzyl bromide (3.21 ml (25.0 mmol) at room temperature for 2 hours. The reaction was worked up by pouring in to 300 ml ice water under continuous stirring. A white precipitate was obtained which was isolated by filtering and

further purified by triturating with ether to give 3.06 g (29%) of the desired product. ^1H NMR (400 MHz, DMSO-d_6) δ 7.65-7.59 (m, 2H), 7.49 (dd, J=8.45, 2.22 Hz, 1H), 7.31 (dt, J= 9.79, 2.22 Hz, 1H), 7.16- 7.08 (m, 2H), 6.05 (d, J= 2.58 Hz, 1H) , 5.93 (d, J= 2.66 Hz, 1H), 5.08 (s, 2H), 1.93 (s, 3H), 1.77 (s, 3H). ES-HRMS m/z 420.0390 (M+H calcd for $C_{20}H_{17}BrF_2NO_2$, requires 420.0411).

Step 3: Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one.



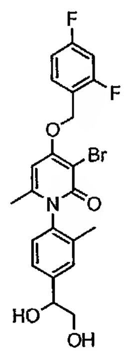
In a 50 ml round bottom flask previously evacuated and filled with nitrogen, 1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2 (1H)-one (0.420 g, 1.0 mmol) was dissolved in dry THF (10 mL). To this mixture was added Pd $(PPh_3)_4$ (0.173 g, 0.15 mmol). The reaction flask was sealed with a rubber septum, evacuated and filled with nitrogen. Under a nitrogen atmosphere, tributyl(vinyl)tin (0.35 ml, 1.2 mmol) was added to the sealed reaction mixture and stirred overnight at 50 °C.

The reaction was worked up by quenching with water and extraction of the product with ethyl acetate. The crude product was purified by column chromatography. Elution with

ethyl acetate-hexanes (50:50 → 0:100) gave 0.32 g (69%) of the desired product.

Step 4: The title compound was prepared by reacting 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one (0.64 g, 1.74 mmol) with N-bromosuccinamide (0.325 g, 1.83 mmol) in acetonitrile (9 mL) at 0°C using a similar procedure as described in step 3 of Example 465, to give 0.423 g (54.5 % after recrystallization) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67(app q, J= 7.59 Hz, 1H), 7.48(s,1H), 7.42(dd, J=8.21,1.98 Hz,1H), 7.33(dt, J=10.00, 2.27 Hz, 1H), 7.17(dt, J=8.51, 2.44 Hz, 1H), 7.13(d, J=7.88 Hz, 1H) 6.74(dd, J=11.29, 6.34 Hz, 1H), 6.67 (s,1H), 5.88(d, J= 17.85, 1H), 5.32-5.30 (m, 2H), 1.92 (s, 3H), 1.88 (s,3H). ES-HRMS m/z 446.0579 (M+H calcd for $C_{22}H_{19}BrF_2NO_2$, requires 446.0568).

Example 478

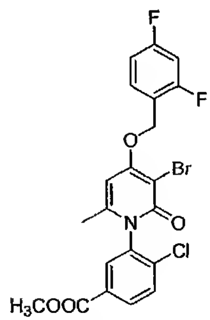


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one (0.126 g, 0.28 mmol) was

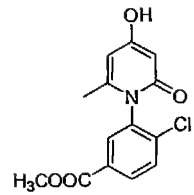
dissolved in a mixture of acetone (3 mL) and water (1 mL). To this was added 4-methylmorpholine N-oxide (0.032 g, 0.28 mmol) and catalytic amount (approximately 5 mgs) of osmium tetroxide was added, and stirred under nitrogen atmosphere. After approximately 2 hours, the reaction was worked up by evaporation of the acetone. The product was extracted into ethyl acetate and concentrated to give a dark colored solid which was further purified by column chromatography to give 0.049 g (37 % yield)of charcoal colored solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (q, J=8.24 Hz, 1H), 7.37-7.23 (m, 3H), 7.17 (dt, J= 8.62, 2.62 Hz, 1H), 7.07 (dd, J=9.36, 2.24 Hz, 1H), 6.65(s,1H), 5.30 (s, 2H), 4.74(t, J=6.16Hz, 1H), 4.57-4.50 (m, 1H), 3.45(app t, J=6.12 Hz, 2H), 3.41- 3.37 (m, 1H), 1.91(s,3H), 1.85 (s, 3H). ES-HRMS m/z 480.0625 (M+H calcd for $C_{22}H_{21}BrF_2NO_4$, requires 480.0623).

Example 479



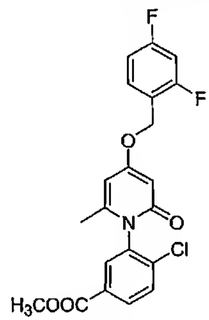
methyl 3-[3-bromo-4-[(2,4-difluorobenzyl) oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoate

Step 1: Preparation of methyl 4-chloro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate.



A condensation reaction with methyl 3-amino-4-chlorobenzoate (14.5g, 78.2 mmol) and 4-hydroxy-6-methyl pyranone under reaction condition similar to the one described in Example 465- step 3 gave 12.32 (53.8%) of desired product.

Step-3- Preparation of methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.

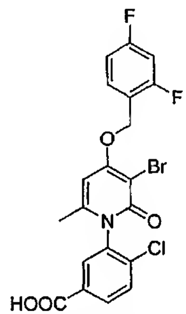


In a 250ml round bottom flask, methyl 4-chloro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (5.28 g, 18.0 mmol) from step1 was reacted with 2,4-difluoro-benzylbromide (3.72 g, 18.0 mmol) in DMF using similar procedure as in Example 472 step 3. After aqueous work up and chromatographic purification, 2.3 g (30%) pure product was obtained.

Step 4: methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoate was prepared by reacting methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (2.3 g, 5.47 mmol) with

N-bromosuccinamide (0.97 g, 5.47 mmol) in acetonitrile (10 mL) at 0°C, using a similar procedure as described in step 3 of Example 465, to give 1.80g (66.2 %) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06-8.03 (m, 2H), 7.86 (d, J=9.70 Hz, 1H), 7.68 (q, J= 7.62, 1H), 7.34(dt, J=10.07, 2.46 Hz, 1H), 7.17 (dt,J= 8.72, 2.90 Hz, 1H), 6.73 (s,1H), 5.33 (s, 2H), 3.85 (s, 3H), 1.91 (s, 3H). ES-MS m/z 495.9757 (M-H calcd for $C_{21}H_{14}BrClF_2NO_4$, requires 495.9795).

Example 480

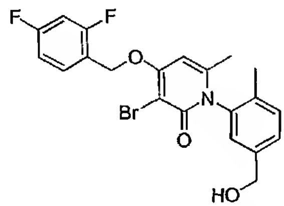


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoic acid

In a 50 ml round bottom flask, methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (0.450 g, 0.90 mmol) was stirred in THF (5 mL). To this mixture was added NaOH (0.120 g, 3.0 mmol) as a solution in water (1.5 mL). The reaction mixture was stirred at room temperature overnight. The THF was evaporated and the residue was acidified with dilute HCl. A white precipitate was obtained. The product was filtered, washed with water and dried in vacuum to give 0.375 g (86 % yield) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, J=7.78, 1.73 Hz, 1H), 7.71-7.65 (m, 2H), 7.53 (d, J=9.08Hz, 1H), 7.33 (dt,

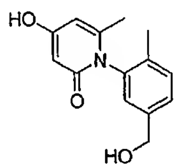
J=9.95, 2.59 Hz, 1H), 7.17 (dt, J=8.22, 2.59 Hz, 1H), 6.68 (s, 1H), 5.32(s, 2H), 1.89 (s,3H). ES-MS m/z 481.9585 (M-H calcd for $C_{20}H_{12}BrClF_2NO_4$, requires 481.9601).

Example 481



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

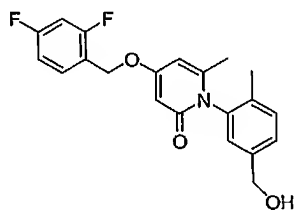
Step 1: Preparation of 4-hydroxy-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl pyridin-2(1H)-one .



4-Hydroxy-6-methyl-2-pyrone (23.0 g, 182.2 mmol) and 3-Amino-4-methylbenzyl alcohol (25.0 g, 182.2 mmol) were taken up in 25 ml of 1,2-dichlorobenzene. The solution was heated to 165°C in a 250 ml round bottom flask equipped with a J-Kem temperature controller probe, and a heating mantle. In a separate 250 ml round bottom flask 4-Hydroxy-6-methyl-2-pyrone (23.0 g, 182.2 mmol) was suspended in 25 ml of 1,2-dichlorobenzene and also heated to 165°C. The pyrone solution was poured into the flask containing the aniline and the reaction stirred at 165°C for 20 minutes. The reaction was allowed to cool to room temperature. Reaction contents were

washed with saturated $NaHCO_3$ (aq.). Separated the organic and aqueous layers. Aqueous layer was made acidic with dropwise addition of concentrated HCl. The product was extracted from the acidic aqueous layer with n-BuOH. N-BuOH removed in vacuo to produce a reddish brown oil. (8.5 g, 19%). Contents carried forward to next reaction with no further purification. ^1H NMR (300 MHz, CD_3OD) δ 7.35 (m, 2H), 7.08 (s, 1H), 6.08 (br s, 1H), 5.81 (br s, 1H), 4.60 (s, 2H), 2.01 (s, 3H), 1.87 (s, 3H). LC/MS, t_r = 1.42 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 246.1131 (M+H). ES-HRMS m/z 246.1107 (M+H calcd for $C_{14}H_{16}NO_3$ requires 246.1125).

Step 2: 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one .

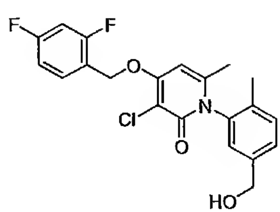


4-hydroxy-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl pyridin-2(1H)-one (from Step 1) (8.0 g, 32.6 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (4.2 ml, 32.6 mmol) and K_2CO_3 (4.5 g, 32.6 mmol) in 50 ml of dimethylformamide. After stirring for 8 hours, H_2O (100 ml) was added to reaction mixture. The product was extracted with ethyl acetate. Ethyl acetate layer was separated and dried over Na_2SO_4. Ethyl acetate was removed in vacuo. A yellow oil was obtained. The oil was passed through a plug of silica gel first eluting with 500 ml of ethyl acetate/hexane

(1:1). This eluent was set aside. Next, ethyl acetate (100%) was passed through the plug until desired product was completely flushed from silica (3 liters). Solvent was removed in vacuo. Light yellow oil obtained (7.5 g, 62%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.60 (app q, J = 6.44 Hz, 1H), 7.42 (d, J = .81 Hz, 2H), 7.15 (s, 1H), 7.06 (m, 2H), 6.21 (dd, J = 1.61, 1.00 Hz, 1H), 6.12 (d, J = 2.62 Hz, 1H), 5.16 (s, 2H), 4.65 (s, 2H), 2.07 (s, 3H), 1.93 (s, 3H); LC/MS, t_r = 2.38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 372 (M+H).

Step 3: Preparation of the title compound . 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one (from Step 2) (4.0 g, 10.8 mmol) was stirred at room temperature with N-bromosuccinimide (2.1 g, 11.9 mmol) in 100 ml of CH_2Cl_2 for 2.0 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed with acetonitrile and dried in vacuo to yield a white solid (3.9 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (app q, J = 6.24 Hz, 1H), 7.35 (d, J = 1.01 Hz, 2H), 7.10 (s, 1H), 7.04 (m, 1H), 6.91 (ddd, J = 11.08, 8.66, 2.42 Hz, 1H), 6.15 (d, J = 0.63 Hz, 2H), 5.29 (s, 2H), 4.66 (s, 2H), 2.08 (s, 3H), 1.97 (s, 3H); ES-MS m/z 450 (M+H). ES-HRMS m/z 450.0467 (M+H calcd for $C_{21}H_{19}BrF_2NO_3$ requires 450.0511).

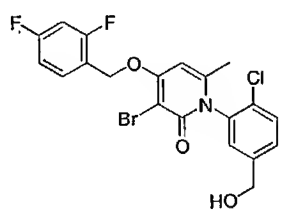
Example 482



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

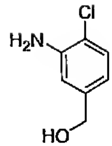
The title compound was prepared by a procedure similar to the one described for Example 481, except that the product from Step 2, Example 481 was chlorinated instead of being brominated. The procedure is as follows: 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one (from Step 2, Example 481 above) (7.0 g, 18.8 mmol) was refluxed with N-chlorosuccinimide (2.5 g, 18.8 mmol) in 50 ml of CH_2Cl_2 overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in MeOH. The precipitate was collected on a filter pad, washed with MeOH and dried in vacuo to yield a white solid (1.6 g, 21%). ^1H NMR (300 MHz, DMF-d_7) δ 7.85 (app q, J = 6.44 Hz, 1H), 7.43 (d, J = 0.81, 1H), 7.42 - 7.23 (m, 3H), 6.84 (s, 1H), 5.48 (s, 2H), 4.67 (s, 2H), 2.05 (s, 3H), 2.03 (s, 3H); ES-MS m/z 406 (M+H). ES-HRMS m/z 406.1033 (M+H calcd for $C_{21}H_{16}ClF_2NO_4$ requires 406.1016).

Example 483



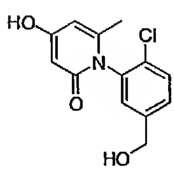
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 3-amino-4-chloro-benzyl alcohol.



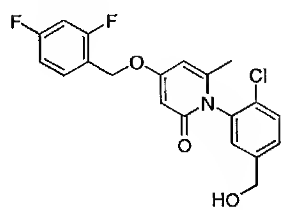
3-Nitro-4-chloro-benzyl alcohol (23.0 g, 122.6 mmol) is taken up in isopropyl alcohol (175 ml) and water (35 ml). Iron powder (<10 micron) (68.0 g, 1.2 moles) and NH_4Cl (66.0 g, 1.2 moles) are added. The suspension is stirred overhead at 70°C in a three neck round bottom flask equipped with a heating mantle and a J-Kem temperature controller probe. After 4 hours, isopropyl alcohol was removed in vacuo. Water (100 ml) and concentrated HCl (10 ml) was added to mixture. Contents are transferred to a separtory funnel and ethyl acetate is used to extract the aqueous layer of impurities. The aqueous layer was then basified with 50% aqueous NaOH. The product was extracted from the basic aqueous layer with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 and then removed in vacuo. The remaining residue was taken up in 50% ethyl acetate/hexane and the precipitate was collected on a filter pad. Precipitate was washed with 50% ethyl acetate/hexane to yield a flocculent brown solid (8.4 g, 44%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.17 (d, J = 8.26 Hz, 1H), 6.86 (d, J = 2.01 Hz, 1H), 6.66 (dd, J = 2.01, 0.61 Hz, 1H), 4.51 (s, 2H); LC/MS, t_r = 0.32 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C); ES-MS m/z 158 (M+H).

Step 2: 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one.



3-amino-4-chloro-benzyl alcohol (8.0g, 51.0 mmol) and 4-hydroxy-6-methyl-2-pyrone (6.4 g, 51.0mmol) were taken up in 1,2-dichlorobenzene (50 ml). The mixture was plunged into a 165°C oil bath where it stirred for 20 minutes. The reaction was cooled to room temperature and the reaction was worked up by washing with saturated $NaHCO_3$ (aq.) and extracting impurities with ethyl acetate. The product remained in the aqueous layer. The basic aqueous layer was made acidic with concentrated HCl. The product was extracted from the acidic aqueous layer with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 and the solvent removed in vacuo. The product was obtained as a yellow oil in a 26% yield and was carried through to the next step with no further purification. ^1H NMR (300 MHz, CD_3OD) δ 7.62 (d, J = 8.26 Hz, 2H), 7.51 (dd, J = 8.46, 2.22 Hz, 1H), 7.36 (d, J = 2.01 Hz, 1H), 6.13 (br s, 1H), 5.84 (d, J = 2.42 Hz, 1H), 4.68 (s, 2H), 1.97 (s, 3H); LC/MS, t_r = 0.25 minutes and 1.41 minutes (tautomer), (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 266 (M+H).

Step 3: 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one .

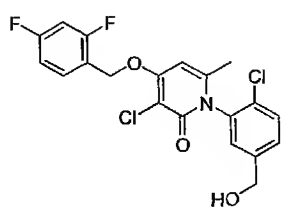


1-[2-chloro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one (from step 2) (3.5g, 13.2 mmol) was taken up in DMF (10 ml) and cooled to 0°C. 2,4-Difluorobenzyl bromide (1.7 ml, 13.2 mmol) and K_2CO_3 (1.8 g, 13.2 mmol) were added and the reaction stirred for 6 hours. The reaction was

worked up by adding saturated $NaHCO_3$ (aq.) and extracting with ethyl acetate. The ethyl acetate extraction was washed with water, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The product was obtained in 83% crude yield and carried through to the next step as a brown oil. LC/MS, t_r = 2.48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 392 (M+H). ES-HRMS m/z 392.0853 (M+H calcd for $C_{20}H_{17}ClF_2NO_3$ requires 392.0860).

Step 4: The title compound was prepared from 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (from step 3) (1.8g, 4.6 mmol) and N-bromosuccinimide (0.82 g, 4.6 mmol) by dissolving them in CH_2Cl_2 (10 ml) and stirring for 2 hours at room temperature. The solvent was removed in vacuo and the residue was taken up in CH_3CN. The precipitate was collected on a filter pad and rinsed with CH_3CN to yield a white solid (370 mg, 17%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (app q, J = 6.24 Hz, 1H), 7.52 (d, J = 8.26 Hz, 1H), 7.40 (dd, J = 8.26, 2.01 Hz 1H), 7.26 (d, J = 0.81 Hz, 1H), 7.03 (m, 1H), 6.91 (ddd, J = 11.08, 8.66, 2.42 Hz, 1H), 6.17 (d, J = 0.81 1H), 5.29 (s, 2H), 4.63 (s, 2H), 2.02 (s, 3H); ES-MS m/z 471 (M+H). ES-HRMS m/z 471.9953 (M+H calcd for $C_{20}H_{16}BrClF_2NO_3$ requires 471.9944).

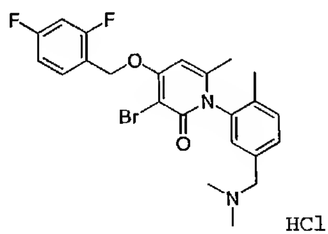
Example 484



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

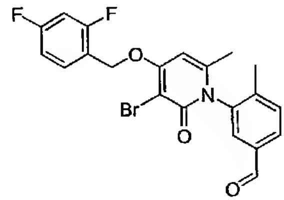
The title compound was prepared from 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2.4 g, 6.1 mmol) and NCS (815.0 mg, 6.1 mmol) in 65°C dichloroethane (20 ml). A catalytic amount of dichloroacetic acid (2 drops) was added. After two hours the solvent was removed in vacuo and the residue was taken up in diethyl ether. The precipitate was collected on a filter pad and then taken up in 50% ethyl acetate/hexanes to remove residual succinimide. The precipitate was collected on a filter pad and then dried in vacuo to produce a white powder (180 mg, 6.9%). . ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (app q, J = 6.44 Hz, 1H), 7.52 (d, J = 8.26 Hz, 1H), 7.40 (dd, J = 8.26, 2.01 Hz 1H), 7.27 (d, J = 2.01 Hz, 1H), 7.00 (m, 1H), 6.91 (m, 1H), 6.20(s, 1H), 5.29 (s, 2H), 4.65 (s, 2H), 2.03 (s, 3H); ES-MS m/z 426 (M+H). ES-HRMS m/z 426.0453 (M+H calcd for $C_{20}H_{16}Cl2F_2NO_3$ requires 426.0470).

Example 485



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(dimethylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1H)-one hydrochloride

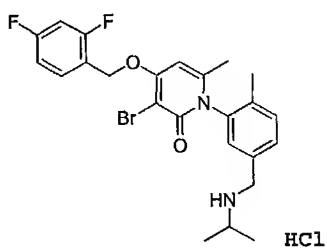
Step 1: Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzaldehyde .



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one (1.5g, 3.33 mmol) was dissolved in 75% CH_3CN/CH_2Cl_2 (20ml) and cooled to 0°C. Dess-Martin Periodinane(2.8 g, 6.66 mmol) was added and the reaction stirred for four hours. At this time, the reaction was quenched with 5% sodium bisulfite (aq.). The product was extracted with ethyl acetate. The combined organic extracts were then washed with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was taken up in diethyl ether and the precipitate was collected on a filter pad and washed with more diethyl ether to yield a white solid (1.35 g, 91%). ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.91 (dd, J = 7.65, 1.61 Hz, 1H), 7.65 (m, 2H), 7.57 (d, J = 7.85 Hz, 1H), 7.03 (m, 1H), 6.95 (ddd, J = 12.69, 8.86, 2.62 Hz, 1H), 6.19 (s, 1H), 5.31 (s, 2H), 2.20 (s, 3H), 1.96 (s, 3H); ES-MS m/z 448 (M+H). ES-HRMS m/z 448.0347 (M+H calcd for $C_{21}H_{17}BrF_2NO_3$ requires 448.0354).

Step 2: Preparation of the title compound . 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzaldehyde (from step 1) (0.50 g, 1.11 mmol) was dissolved in CH_2Cl_2 (10 ml). N,N-dimethylamine (2.0 M in THF)

(1.11 ml, 2.22 mmol) was added. This mixture stirred for at room temperature for 12 hours. Next, sodium tri-acetoxyborohydride (0.47 g, 2.22 mmol) was added and the reaction stirred for two more hours. The reaction was washed with 1 N NaOH (aq.) and then extracted with CH_2Cl_2. The combined organic extracts were washed with water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was taken up in diethyl ether. 1M HCl in diethyl ether (5 ml) was added and the precipitate was collected on a filter pad. This precipitate was hygroscopic. The hygroscopic solid was then taken up in hot ethyl acetate. Hexane was added until a precipitate crashed out. The precipitate was collected on a filter pad to yield a white solid (150 mg, 26%). ^1H NMR (400 MHz, D_2O) δ 7.42 (m, 3H), 7.17 (s,1H), 6.86 (m, 2H), 6.53(s, 1H), 5.20(s, 2H), 4.18(s, 1H), 2.72(s, 6H), 1.85(s, 3H), 1.82(s, 3H); ES-MS m/z 477 (M+H). ES-HRMS m/z 477.0955 (M+H calcd for $C_{23}H_{24}BrF_2N_2O2$ requires 477.0984).



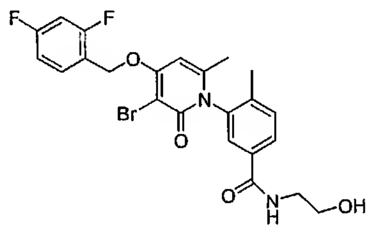
Example 486

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(isopropylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1H)-one hydrochloride

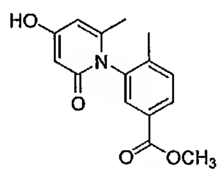
The title compound was prepared by reductive amination of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-

1(2H)-yl]-4-methylbenzaldehyde (from step 1) (0.50 g, 1.11 mmol) with iso-propyl amine (0.13 g, 2.22) according to the procedure described above for Example 485 (Step 2) to give the desired compound (0.49g, 84%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (app quartet, J = 6.58 Hz, 1H), 7.53 (m, 2H), 7.29(br s, 1H), 7.03(m, 1H), 6.68 (s, 1H), 5.36 (s, 2H), 4.22(s, 2H), 3.46(m, 1H), 2.06 (s, 3H), 2.01 (s, 3H), 1.37 (d, J = 6.58 Hz, 6H) ; ES-MS m/z 491 (M+H). ES-HRMS m/z 491.1107 (M+H calcd for $C_{24}H_{26}BrF_2N_2O2$ requires 491.1140).

Example 487



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide

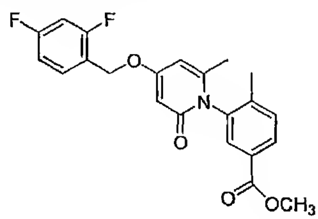


Step 1: Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate .

4-Hydroxy-6-methyl-2-pyrone (22.9 g, 181.6 mmol) and methyl-3-amino-2-methylbenzoate (25 g, 151.3 mmol) were suspended in 50 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle.

The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 110°C. At this point, 200 ml of toluene was added. The flask was plunged into a 0°C ice bath while stirring. "Oiling out" occurred. Perhaps too much toluene was added so some of the solvent was removed in vacuo. The oil went back into solution and a light brown precipitate remained. The toluene mixture was allowed to stir for 72 hours at room temperature. A precipitate was collected on a filter pad. The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C. water to remove excess pyrone, and dried in vacuo to give a tan solid (16.5 g, 40% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.06 (dd, J = 8.06, 1.61 Hz, 1H), 7.80 (d, J = 1.61 Hz, 1H), 7.56 (d, J = 8.06, Hz, 1H), 6.15 (dd, J = 2.42, 0.81 Hz, 1H), 5.86 (d, J = 2.42 1H), 3.94 (s, 3H), 2.15 (s, 3H), 1.91 (s, 3H); ES-MS m/z 274 (M+H). ES-HRMS m/z 274.1066 (M+H calcd for $C_{15}H_{16}NO_4$ requires 274.1074).

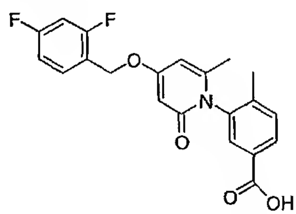
Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate .



Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate (from Step 1) (16.5 g, 60.4 mmol) 2,4-difluorobenzyl bromide (7.8 ml, 60.4 mmol) were taken up in 250 ml of N,N-dimethylformamide and the mixture was cooled to 0°C. K_2CO_3 (8.3g, 60.4 mmol) was added and reaction stirred for 12 hours during which time the reaction was allowed to

warm to room temperature. LC/MS indicated the presence of starting material after 12 hours. An excess of K_2CO_3 was added at room temperature along with 0.50 ml of 2,4-difluorobenzyl bromide. The reaction stirred for an additional two hours. Saturated $NaHCO_3$ (aq.) was poured into reaction vessel. The solution was extracted with ethyl acetate and the organic layers were combined then washed with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4, and evaporated. The product was carried on to the next step as a crude oil (24.1 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.85, 1.61 Hz, 1H), 7.82 (d, J = 1.61, 1H), 7.52-7.44 (m, 2H), 7.01 - 6.88 (m, 2H), 6.05 (d, J = 2.62 Hz, 1H), 5.97 (dd, J = 2.62, 0.81 Hz, 1H), 5.08 (s, 2H), 3.93 (s, 3H), 2.20 (s, 3H), 1.89 (s, 3H); ES-MS m/z 400 (M+H). ES-HRMS m/z 400.1374 (M+H calcd for $C_{22}H_{20}F_2NO_4$ requires 400.1355).

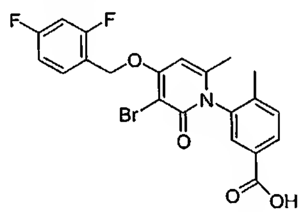
Step 3: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (14g, 35.0 mmol)(from step 2) was taken up in THF (25 ml) and H_2O. 2.5 N NaOH (aq.) was added and the reaction stirred for 30 minutes at room temperature. The reaction was made acidic via the addition of concentrated HCl. The product was extracted with ethyl acetate. The ethyl acetate extraction was dried over Na_2SO_4,

filtered, and the solvent removed in vacuo. Upon vacuum removal of the solvent, the product crashed out of the ethyl acetate. This precipitate was collected on a filter pad and washed with a 50 ethyl acetate/hexanes to yield a white powder (9g, 7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, J = , 1.61 Hz, 1H), 7.84 (d, J = 1.61 Hz, 1H), 7.52 - 7.47 (app q, J = 8.26, 1H), 7.43 (d, J = 8.06 Hz, 1H), 7.00 - 6.88 (m, 2H), 6.19 (d, J = 2.62 Hz, 1H), 6.05 (dd, J = 2.62, 1.81 Hz, 1H), 5.17 (s, 2H), 2.19 (s, 3H), 1.90 (s, 3H); ES-HR/MS m/z 386.12 (M+H calcd for $C_{21}H_{18}F_2NO_4$ requires 386.1198).

Step 4: Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .

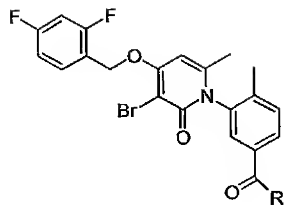


3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (5.9 g, 15.2 mmol) (from step 3 above) was taken up in dichloromethane (25 ml). N-Bromosuccinimide was added and the reaction stirred for 14 hours. The dichloromethane was removed in vacuo and the residue was taken up in acetonitrile. The precipitate was collected on a filter pad and rinsed with acetonitrile to yield the desired product as a white solid (5.2 g, 74%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.87 (dd, J = 7.85, 1.61,Hz, 1H), 7.82 (d, J = 1.81 Hz, 1H), 7.69 (app q, J = 8.06 Hz 1H), 7.57 (d, J = 8.06 Hz, 1H), 7.09 (dt, J = 8.66, 2.22 Hz, 1H), 6.70 (s, 1H), 5.40 (s, 2H), 2.14 (s, 3H), 2.02 (s, 3H); ES-MS m/z 464

(M+H). ES-HRMS m/z 464.0275 (M+H calcd for $C_{21}H_{17}BrF_2NO_4$ requires 464.0304).

Step 5: Preparation of the title compound. 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from Step 4 above) (1.9g, 4.10 mmol) was dissolved in 20 ml of CH_2Cl_2. Ethanolamine (297 µl, 4.92 mmol) was added, followed, in order, by EDCI (0.764 g, 4.92 mmol), 1-hydroxybenzotriazole (0.665g, 4.92 mmol) and triethylamine (1.14 ml, 8.20 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate. The combined organic layer was then washed with saturated $NaHCO_3$ (aq.) and extracted 3 times with ethyl acetate. The organic layers were combined and washed with H_2O and extracted 3 times with ethyl acetate. The organic layers were combined and dried over Na_2SO_4 and evaporated. The resulting residue was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (1.5g, 72%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.85, 1.61 Hz, 1H), 7.65 (d, J = 1.61 Hz, 1H), 7.62 (app q, J = 8.26 Hz, 1H), 7.40 (d, J = 8.06 Hz, 1H), 7.39 - 7.30 (m, 1H), 7.03 - 6.97 (m, 1H), 6.88 - 6.81 (m, 1H), 6.25 (s, 1H), 5.20 (s, 2H), 3.70 - 3.52 (m, 1H), 3.16 - 3.12 (m, 2H), 2.10 (s, 3H), 1.98 (s, 3H); ES-MS m/z 507 (M+H). ES-HRMS m/z 507.0719 (M+H calcd for $C_{23}H_{22}BrF_2N_2O_4$ requires 507.0726).

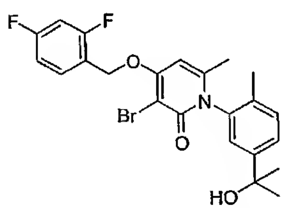
Examples 488-491



The compounds of Examples 488-491-476 are prepared essentially according to the procedures set forth for Example 487.

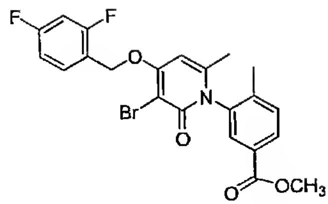
Compound No.	R	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 488	$-NH(CH_2)_2OCH_3$	84	$C_{24}H_{24}BrF_2N_2O_4$	528.0882	521.0868
Ex. 489	$-NHCH_3$	79	$C_{22}H_{20}BrF_2N_2O_3$	477.0620	477.0602
Ex. 490	$-N(CH_3)_2$	54	$C_{23}H_{22}BrF_2N_2O_3$	491.0776	491.0753
Ex. 491	-morpholine	65	$C_{25}H_{24}BrF_2N_2O_4$	533.0858	533.0882

Example 492



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate.

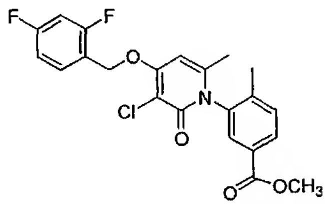


Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (as prepared above) (1.8g, 4.51 mmol) was taken up in CH_2Cl_2 (10 ml). N-bromosuccinimide (0.80 g, 4.51 mmol) was added and the mixture stirred at room temperature for two hours. The CH_2Cl_2 is removed in vacuo and the residue is taken up in CH_3CN. The resulting precipitate is collected on a filter pad and washed with CH_3CN to yield a white solid (0.30 g, 14%, first crop). ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.06, 1.61 Hz, 1H), 7.80 (d, J = 1.61 Hz, 2H), 7.65 (app q, J = 8.46 Hz, 1H), 7.48 (d, J = 8.06, 1H), 7.05 - 6.99 (m, 1H), 6.96 - 6.89 (m, 1H), 6.16 (s, 1H), 5.31 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H), 1.96 (s, 3H). ES-HRMS m/z 478.0476 (M+H calcd for $C_{22}H_{19}BrF_2NO_4$ requires 478.0476).

Step 2: Preparation of the title compound. Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (0.22 g, 0.46 mmol) was taken up in THF and cooled to 0°C. MeMgCl (3.0 M in THF) (0.73 ml, 2.2 mmol) was slowly added to the 0°C solution. The reaction was allowed to proceed without maintaining the 0°C bath temperature. The reaction was complete within two hours. At this time the mixture was quenched with saturated NH_4Cl (aq.) and extracted with ethyl acetate. The organic layers were combined, washed with H_2O, and extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4, filtered, and evaporated. The residue was taken up in 50% ethyl acetate/hexanes. The

precipitate was collected on a filter pad and washed with 50% ethyl acetate/hexanes to yield a white solid (0.10 g, 45%). ^1H NMR (300 MHz, CD_3OD) δ 7.70 (app q, J = 8.26, Hz, 1H), 7.54 (dd, J = 8.06, 2.01 Hz, 1H), 7.40 (d, J = 1.81 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.68 (s, 1H), 5.40 (s, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.57 (s, 6H). ES-HRMS m/z 478.0785 (M+H calcd for $C_{23}H_{23}BrF_2NO_3$ requires 478.0824).

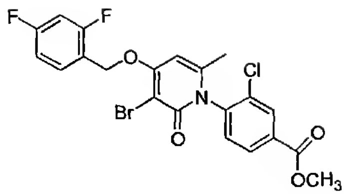
Example 493



methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate

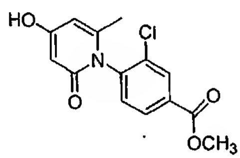
The title compound was prepared by taking up methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (1.46g, 3.66 mmol) in dichloroethane (25 ml) and adding N-chlorosuccinimide (0.49g, 3.66 mmol), dichloroacetic acid (catalytic), and heating to 50°C for 6 hours. At this time, the solvent was removed in vacuo and the residue taken up in diethyl ether. The precipitate was collected on a filter pad. ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.85, 1.61 Hz, 1H), 7.80 (d, J = 1.81 Hz, 2H), 7.62 (app q, J = 8.46 Hz, 1H), 7.48 (d, J = 7.85, 1H), 7.05 - 6.95 (m, 1H), 6.93 - 6.89 (m, 1H), 6.19 (s, 1H), 5.30 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H), 1.97 (s, 3H). ES-HRMS m/z 434.0932 (M+H calcd for $C_{22}H_{19}ClF_2NO_4$ requires 434.0965).

Example 494



methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate

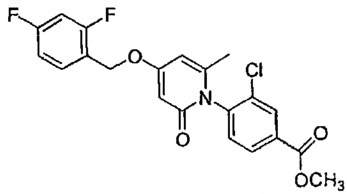
Step 1: Preparation of methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate .



4-Hydroxy-6-methyl-2-pyrone (24.5 g, 193.9 mmol) and methyl-3-amino-2-chlorobenzoate (30 g, 161.6 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 175°C for 20 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 110°C. At this point, 200 ml of toluene was added. The toluene mixture was allowed to stir for 72 hours at room temperature. A precipitate was collected on a filter pad. The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C. water to remove excess pyrone, and dried in vacuo to give a tan solid (13.0 g, 27% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.26 (d, J = 1.81 Hz, 1H), 8.14 (dd, J = 8.26, 1.81 Hz, 1H),

7.54 (d, J = 8.26, Hz, 1H), 6.14(dd, J = 2.42, 1.0 Hz, 1H), 5.83 (d, J = 2.42 1H), 4.00 (s, 3H), 1.96 (s, 3H); LC/MS, t_r = 1.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

Step 2: Preparation of methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .

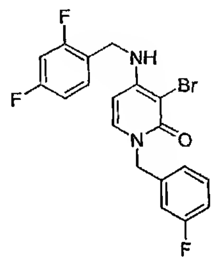


Methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (from Step 1) (2.4g, 8.17 mmol) was taken up in DMF (10 ml). 2,4-difluorobenzylbromide (1.05 ml, 8.17 mmol) and K_2CO_3 (1.13 g, 8.17 mmol) were added. The reaction stirred for 6 hours at room temperature. At this time, the reaction was poured into water (200 ml) and extracted with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4, filtered, and the solvent removed in vacuo to give amber oil (2.62 g, 77% crude yield). LC/MS, t_r = 2.79 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

Step 3: Preparation of the title compound . Methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 2) (2.60g, 6.21 mmol) was taken up in CH_2Cl_2 (20 ml). N-bromosuccinimide (1.11g, 6.21 mmol) was added and the mixture stirred at room temperature for 4 hours. The CH_2Cl_2 is removed in vacuo and the residue is taken up in CH_3CN. The resulting precipitate is collected on a filter pad and washed with CH_3CN to yield a white solid (0.75 g, 24%). ^1H

NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 1.88 Hz, 1H), 8.06 (dd, J = 8.19, 1.75 Hz, 1H), 7.59 (app q, J = 8.46 Hz, 1H), 7.33 (d, J = 8.19, 1H), 6.96 (dt, J = 8.06, 1.21 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.13 (s, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 1.95 (s, 3H). ES-HRMS m/z 497.9892 (M+H calcd for $C_{22}H_{16}BrClF_2NO_4$ requires 497.9914).

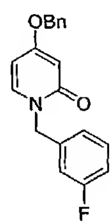
Example 495



3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one

Step 1

Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one

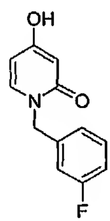


A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 4-benzyloxy-2(1H)-pyridinone (20 g, 99.6 mmol) and N,N-dimethyl formamide (50 mL). K_2CO_3 (13.7 g, 99.6 mmol) and KI (1.6 g, 9.6 mmol) were added followed by 3-fluorobenzyl bromide (14.6 mL, 119.4 mmol). The reaction mixture was heated for 18 h at 80 C. The reaction

mixture was concentrated in vacuo and treated with hot ethyl acetate. The solids were filtered off, the filtrate was poured into water and was extracted with ethyl acetate. The organic extract was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in hot ethyl acetate and precipitated with hexanes to give the title compound (10 g, 33%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, J = 8.4 Hz, 1H), 7.37 (m, 5H), 7.07 (d, J = 8.4 Hz, 1H), 7.01 (app d, J = 8.4 Hz, 2H), 6.17 (d, J = 2.68 and 7.6 Hz, 1H), 6.04 (d, J = 2.68 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -114.88 (1 F) ppm. ES-HRMS m/z 310.1271 (M+H calcd for $C_{19}H_{17}FNO_2$ requires 310.1238).

Step 2

Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one

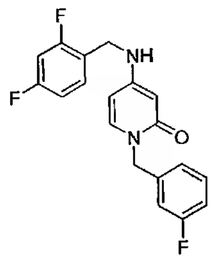


A small Parr bottle was charged with SC-82484 (10 g, 32.3 mmol), ethanol (175 mL) and10% Pd/C (0.5 g). The system was flushed twice with both nitrogen and hydrogen. The reaction mixture was hydrogenated at 30 psi until no starting material was visible by LC-MS. The reaction mixture was slurried with Celite and then was filtered through a pad of celite. The filtrate and ensuing ethanol washes were concentrated in vacuo to give a beige solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, J = 7.67 Hz, 1H), 7.32 (m, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.05 (dd, J = 2.58 and 7.67 Hz, 1H), 5.83 (d,

J = 2.0 Hz, 2H), 5.10 (s, 2H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -115.33 (1 F) ppm. ES-HRMS m/z 218.0641 (M+H calcd for $C_{12}H_{11}FNO_2$ requires 218.0612).

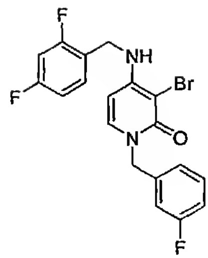
Step 3

Preparation of 4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one



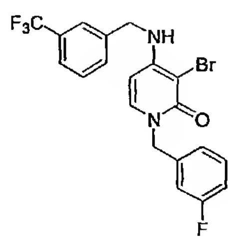
The product from Step 2 (0.5 g, 2.28 mmol) and 2,4-difluoro benzylamine (4 mL, 33.6 mmol) were combined in a nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was chromatographed on silica (95:5 ethyl acetate: methanol). The final compound was isolated as a light yellow solid (0.16 g, 36%). ^1H NMR (400 MHz, CD_3OD) δ 7.33 (m, 3H), 7.03 (d, J = 8 Hz, 1H), 6.96 (m, 3H), 6.95 (m, 1H), 5.97 (dd, J = 3.2 and 8.0 Hz, 1 H), 5.48 (d, J = 2.56 Hz, 1H), 5.02 (s, 2H), 4.33 (s, 2H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -113.88 (1 F), -115.33 (1F), -116.78 (1F) ppm. ES-HRMS m/z 345.1221 (M+H calcd for $C_{19}H_{17}F_3N_2O$ requires 345.1209).

Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one



N-Bromo succinimide (81 mg, 0.46 mmol) was added to a solution of the product from Step 3 (0.15 g, 0.44 mmol) in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction was complete by LC-MS. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. ^1H NMR (400 MHz, $CDCl_3$) δ 7.3-7.2 (m, 4H), 7.07 (app t, J = 7.6 Hz, 2H), 6.97 (m, 2H), 6.80 (m, 2H), 5.78 (d, J = 7.6 Hz, 1H), 5.30 (br s, 1H), 5.08 (s, 2H), 4.46 (d, J = 6 Hz, 2H) ppm. ^{19} F NMR (400 MHz, $CDCl_3$) δ -110.64 (1 F), -112.75 (1F), -114.79 (1F) ppm. ES-HRMS m/z 423.0275 (M+H calcd for $C_{19}H_{15}BrF_3N_2O$ requires 423.0314).

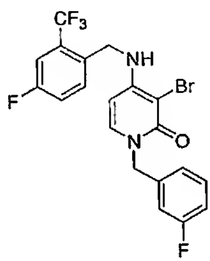
Example 496



3-bromo-1-(3-fluorobenzyl)-4-{[3-(trifluoromethyl)benzyl]amino}pyridin-2(1H)-one

The title compound was prepared essentially as in Example 495. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.48 (m, 2H), 7.27 (q, J = 3.1, 9.0 Hz, 1H), 6.96 (app t, J = 8.8 Hz, 2H), 5.71 (d, J = 7.6 Hz, 1H), 5.4 (br m, 1H), 5.08 (s, 2H), 4.52 (d, J = 5.6 Hz, 2H) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -63 (3 F), -112 (1 F) ppm. ES-HRMS m/z 455.0388 (M+H calcd for $C_{20}H_{16}BrF_4N_2O$ requires 455.0377).

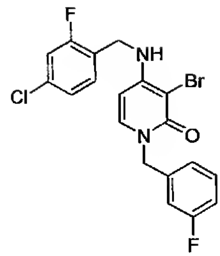
Example 497



3-bromo-1-(3-fluorobenzyl)-4-{[4-fluoro-2-(trifluoromethyl)benzyl]amino}pyridin-2(1H)-one

The title compound was prepared essentially as in Example 495. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.27 (m, 3H), 7.07 (m, 2H), 6.99 (m, 2H), 5.65 (d, J = 10Hz, 1H), 5.46 (br s, 1H), 5.09 (s, 2H), 4.64 (s, 2H) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -61.31 (3 F), -112.69 (1 F), 112.97 (1F) ppm. ES-HRMS m/z 473.0246 (M+H calcd for $C_{20}H_{15}BrF_5N_2O$ requires 473.0282).

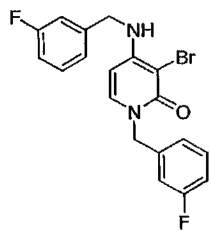
Example 498



Preparation of -bromo-4-[(4-chloro-2-fluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one

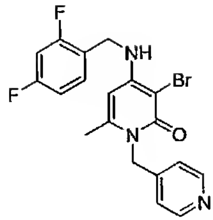
The title compound was prepared essentially as in Example 495. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.19 (app t, J = 8.8 Hz, 1H), 7.10 (m, 4H), 6.95 (app t, J = 8.8 Hz, 2H), 5.74 (d, J = 8 Hz, 1H), 5.40 (br s, 1H), 5.08 (s, 2H), 4.47 (d J = 6 Hz, 2H) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -112.67 (1 F), -116.39 (1 F) ppm. ES-HRMS m/z 439.0047 (M+H calcd for $C_{19}H_{15}ClBrF_2N_2O$ requires 439.0019).

Example 499



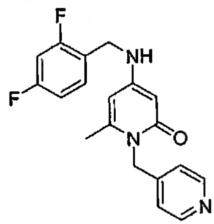
The title compound was prepared essentially as in Example 495. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35- 7.2 (m, 1H), 7.27 (dd, J = 2.5 and 8 Hz, 1H), 7.05 (app d, J = 7.2 Hz, 3H), 6.97 (m, 4H), 5.72 (d, J = 7.6 Hz, 1H), 5.41 (br s, 1H), 5.08 (s, 2H), 4.46 (d, J = 6.4 Hz, 2H) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -112.5 (1 F), -113 (1 F) ppm. ES-HRMS m/z 405.0431 (M+H calcd for $C_{19}H_{16}BrF_2N_2O$ requires 405.0409).

Example 500



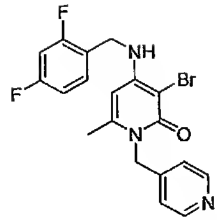
Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one.

Step 1 Preparation of 4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



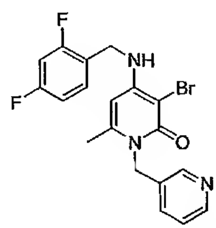
(0.3 g, 1.39 mmol) and 2,4-difluoro benzylamine (1 mL, 8.4 mmol) were combined in a nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo. ^1H NMR (400 MHz, CD_3OD) δ 8.44 (dd, J = 1.7 and 4.8Hz, 2H), 7.38 (q, J = 10 and 15 Hz, 1H), 7.14 (d, J = 4.8 Hz, 2H), 6.95 (m, 2H), 5.90 (dd, J = 1 and 2.5Hz, 1H), 5.47 (d, J = 2, 1H), 5.28 (s, 2H), 4.33 (s, 2H), 2.27 (s, 3H) ppm. ^{19} F NMR (400 MHz, CD_3OD) δ -113.73 (1 F), -116.66 (1 F) ppm. ES-HRMS m/z 342.1422 (M+H calcd for $C_{19}H_{18}F_2N_3O$ requires 342.1418).

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



N-Bromo succinimide (77 mg, 0.43 mmol) was added to a solution of the product of Step 1 (0.14 g, 0.41 mmol) in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction was complete by LC-MS. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was triturated with hexanes to give the title compound as a yellow solid (81 mg, 47 %). ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, J = 1.6 and 4.8Hz, 2H), 7.24 (q, J = 6.4 and 13.6 Hz, 1H), 7.01 (d, J = 6.4 Hz, 2H), 6.83 (m, 2H), 5.68 (s, 1H), 5.25 (s, 2H), 4.45 (d, J = 6.4Hz, 2H), 2.12 (s, 3H) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -110.51 (m, 1 F), -114.66 (m, 1 F) ppm. ES-HRMS m/z 420.0524 (M+H calcd for $C_{19}H_{17}BrF_2N_3O$ requires 420.0523).

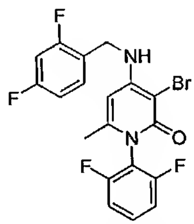
Example 501



Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

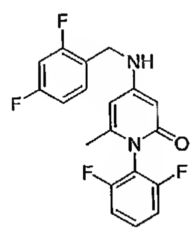
The title compound was prepared essentially as in Example 500. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.8Hz, 2H), 7.55 (app t, J = 6 Hz, 1H), 7.21 (m, 2H), 6.83 (m, 2H), 5.65 (s, 1H), 5.34 (d, J = 5.2Hz, 1H), 5.27 (s, 2H), 4.45 (s, 2H), 2.10 (d, J = 4.8Hz, 3H) ppm. ^{19}F NMR (400 MHz, $CDCl_3$) δ -110.74 (1 F), -114.86 (1 F) ppm. ES-HRMS m/z 420.0533 (M+H calcd for $C_{19}H_{17}BrF_2N_3O$ requires 420.0523).

Example 502



Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

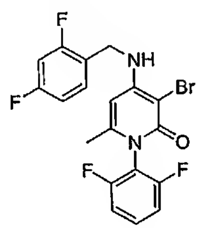
Step 1 Preparation of 4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one



1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.3 g, 1.26 mmol) and 2,4-difluoro benzylamine (1mL, 8.4 mmol) were combined in a nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was

chromatographed on silica (1:1 hexanes: ethyl acetate). The compound was approximately 50% pure and was carried on without further purification (0.633 g). ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (m, 1H), 7.41 (m, 1H), 7.16 (t, J = 8.8Hz, 2H), 6.93 (m, 2H), 6.00 (s, 1H), 5.42 (s, 1H), 5.42 (s, 1H), 4.37 (s, 2H), 1.93 (s, 3H) ppm. LC/MS, t_r = 4.65 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 363 (M+H).

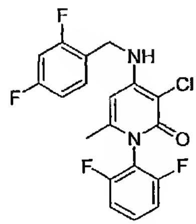
Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one



N-Bromo succinimide (168 mg; 0.945 mmol) was added to a solution of the product of Step 1 (0.633 g) in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction was 50 % complete by LC-MS. Additional N-bromo succinimide (150 mg) was added and the reaction was stirred at 25 C for 12 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by reverse phase chromatography (60:40 Acetonitrile: water with 0.05% trifluoroacetic acid). The title compound was isolated as the TFA salt (0.161g, 23%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (m, 1H), 7.35 (q, J = 8, 15.6Hz, 1H), 7.16 (t, J = 8 Hz, 2H), 6.96 (app q, J = 8, 16.4Hz, 2H), 6.12 (s, 1H), 4.86 (s, 2H), 1.94 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -

77.33 (1 F), -113.60 (1 F), -116.63 (1F), -121.50 (1F) ppm. ES-HRMS m/z 441.0231 (M+H calcd for $C_{19}H_{14}BrF_4N_2O$ requires 441.0220).

Example 503

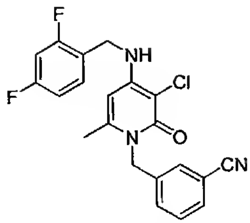


Preparation of 3-chloro-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.3 g, 1.26 mmol) and 2,4-difluoro benzylamine (1mL, 84 mmol) were combined in an nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was used without further purification. N-Chloro succinimide (168 mg, 1.26 mmol) was added to a solution of the residue in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica (25:75 hexanes: ethyl acetate) to give the title compound (32 mg, 6%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (m, 1H), 7.36 (q, J = 9.2 and 15.2Hz, 1H), 7.18 (t, J = 7.6Hz, 2H), 6.98 (m, 2H), 6.15 (s, 1H), 4.62 (s, 2H), 1.96 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -113.78 (1 F), -116.72 (1 F), -121.57

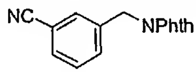
(1F) ppm. ES-HRMS m/z 397.0752 (M+H calcd for $C_{19}H_{14}ClF_4N_2O$ requires 397.0725).

Example 504



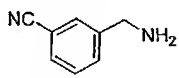
Preparation of 3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

Step 1 Preparation of 3-phthalimidomethyl-benzonitrile



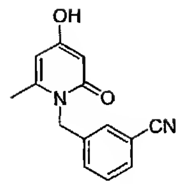
3-Phthalimidomethyl-benzonitrile was prepared as described in the literature. (Bookser, B.C.; Bruice, T.C. J. Am. Chem. Soc. 1991, 113, 4208-18.)

Step 2 Preparation of 3-(aminomethyl)benzonitrile



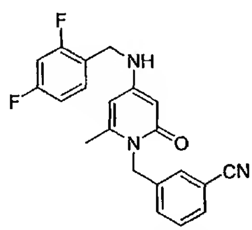
3-(Aminomethyl)benzonitrile was prepared as described in the literature. (Bookser, B.C.; Bruice, T.C. J. Am. Chem. Soc. 1991, 113, 4208-18.)

Step 3 Preparation of 3-[(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)methyl]benzonitrile



A nitrogen flushed pyrex reaction tube was charged with 3-(aminomethyl)benzonitrile (1 g, 7.9 mmol), 4-hydroxy-6-methyl-2-pyrone (1 g, 7.9 mmol) and water (20 mL). The tube was capped and was heated to reflux. After 1.5 h, the product precipitated from solution. The reaction mixture was cooled to room temperature, filtered and washed with water. The product was used without further purification (1.67g, 88 %). ^{1}H NMR (400 MHz, dmso-d_6) δ 10.53 (s, 1H), 7.61 (d, J = 8Hz, 1H), 7.52 (t, J = 8Hz, 2H), 7.38 (d, J = 8 Hz, 1H), 5.79 (dd, J = 1 and 2.5 Hz, 1H), 5.56 (d, J = 2.7 Hz, 1H), 5.18 (s, 2H), 2.14 (s, 3H) ppm. ES-HRMS m/z 241.0968 (M+H calcd for $C_{14}H_{13}N_2O_2$ requires 241.0972).

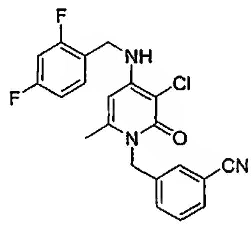
Step 5 Preparation of 3-{[4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The product from Step 4 (0.5 g, 2.08 mmol) and 2,4-difluoro benzylamine (2mL, 16.8 mmol) were combined in a nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was triturated with ethyl acetate/ hexanes to precipitate the starting materials. The residue was

chromatographed on reverse phase (1:1 water: acetonitrile with 0.05% trifluoroacetic acid). The product of Step 5 was isolated as a white semi-solid (0.125g, 15%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61(d, J = 8Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.41 (m, 3H), 6.94 (m, 2H), 5.89 (dd, J = 0.8 and 2.7Hz, 1H), 5.47 (d, J = 2.8Hz, 1H), 5.27 (s, 2H), 4.34 (s, 2H), 2.18 (s, 3H) ppm. LC/MS, t_r = 4.87 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 366 (M+H).

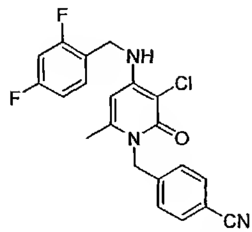
Step 6 Preparation of 3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



N-Chloro succinimide (36 mg, 0.27 mmol) was added to a solution of the product of Step 5 (0.125 g, 0.26 mmol) in methylene chloride (10 mL). After stirring at 25 C for 2 h, the reaction was complete by LC-MS. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was triturated with acetonitrile to give the title compound as a tan solid (20 mg, 13%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, J = 8.4 Hz, 1H), 7.49 (m, 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.33 (q, J = 8.4 and 14.8 Hz, 1H), 6.94 (m, 2H), 6.00 (s, 1H), 5.34 (s, 2H), 4.56 (s, 2H), 2.21 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -114.00 (1 F), -116.89 (1 F)

ppm. LC/MS, t_r = 5.49 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 400 (M+H).

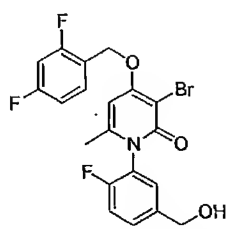
Example 505



Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

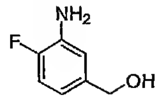
The title compound was prepared essentially as in Example 504. ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 8 Hz, 2H), 7.33 (q, J =8 and 15.2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 6.94 (m, 2H), 6.01 (s, 1H), 5.36 (s, 2H), 4.55 (s, 2H), 2.19 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -77.52 (1F), -113.89 (1 F), -116.71 (1 F) ppm. LC/MS, t_r = 5.49 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 400 (M+H).

Example 506



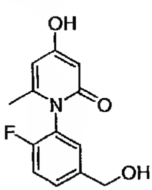
Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

Step 1 Preparation of (3-amino-4-fluorophenyl)methanol



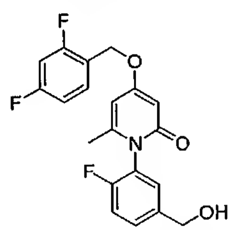
A flask equipped with overhead stirrer was charged with 4-fluoro-3-nitrobenzyl alcohol (20g, 0.117 mol) and 200 mL of 5:1 isopropanol: water. Ammonium chloride (62 g, 1.17 mol) was added followed by iron filings (65g, 1.17 mol). The mixture was stirred at 70 C for 1.5 H when it was shown to be complete by LC-MS. The liquid was decanted and the solids were washed with additional isopropanol: water. The isopropanol was removed and the residue was diluted with 0.5 N HCl and was extracted with ethyl acetate. The aqueous layer was brought to pH 12-14 with 2.5 N NaOH and was extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. 3-Amino-4-fluorophenyl methanol was isolated as a brown solid (4.5g, 27%) and was used without further purification. LC/MS, t_r = 2.40 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 142 (M+H). ES-HRMS m/z 142.0692 (M+H calcd for C_7H_8FNO requires 142.0663).

Step 2 Preparation of 1-[2-fluoro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one



A 100 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with (3-amino-4-fluorophenyl)methanol (4.5 g, 31.9 mmol), 4-hydroxy-6-methyl-2-pyrone (4 g, 31.9 mmol) and o-dichlorobenzene (5 mL). The system was immersed in a 170 C oil bath for 10 minutes. The solvent was removed in vacuo and the residue was chromatographed on reverse phase (75:25 water:acetonitrile with 0.05% TFA). The product contained some starting materials after purification and was used without further purification (1.27g, 15%). ^{1}H NMR (400 MHz, dmso-d_6) δ 7.39 (m, 1H), 7.20 (dd, J = 2.2 and 7.6 Hz, 1H), 6.74 (dd, J = 2.7 and 9.6 Hz, 1H), 5.93 (dd, J = 1.2 and 2.2 Hz, 1H), 5.22 (dd, J = 0.4 and 2.2 Hz, 1H), 2.12 (s, 3H) ppm. ES-HRMS m/z 250.0862 (M+H calcd for $C_{13}H_{13}FNO_3$ requires 250.0874).

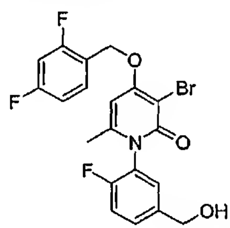
Step 3 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one



A 100 mL roundbottomed flask (nitrogen purged) was charged with 1-[2-fluoro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one (1.2g, 4.82 mmol) and N,N-dimethyl formamide (10 mL). Potassium carbonate (0.6g, 4.4 mmol) and 2,4-difluorobenzyl bromide (0.56 mL, 4.4 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic

layer was concentrated in vacuo and the residue was chromatographed on silica (9:1 methylene chloride: ethanol). The impure oil (0.3g, 17%) was carried on without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (m, 2H), 7.30 (m, 2H), 7.02 (m, 2H), 6.17 (dd, J = 1 and 2.8 Hz, 1H), 6.03 (d, J = 2.8 Hz, 1H), 5.14 (s, 2H), 4.62 (s, 2H), 2.14 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.35 (1F), -115.97 (1 F), -127.31 (1 F) ppm. LC/MS, t_r = 5.05 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 375 (M+H).

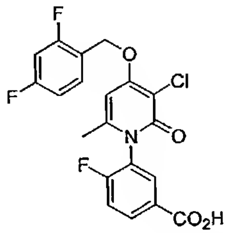
Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one



N-Bromo succinimide (50 mg, 0.3 mmol) was added to a solution of the product of Step 3 (0.12 g, 0.32 mmol) in N,N-dimethyl formamide (4 mL). After stirring at 25 C for 2 h, trifluoroacetic acid (50 µL) was added. After 1 h, additional N-Bromo succinimide (30 mg) was added. After 1 h, the reaction was complete by LC-MS. The reaction mixture was poured into brine and was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on reverse phase (95:5 methylene chloride: ethanol). The title compound was isolated as the TFA salt (38 mg, 26 %). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (q, J = 7.6 and 14.8 Hz, 1H), 7.51 (m, 1H), 7.31 (app t, J = 8.4 Hz, 1H), 7.04 (t,

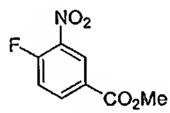
J = 8.4 Hz, 2H), 6.63 (s, 1H), 5.34 (s, 2H), 4.62 (s, 2H), 2.06 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.48 (1F), -115.92 (1 F), -127.23 (1 F) ppm. ES-HRMS m/z 454.0228 (M+H calcd for $C_{20}H_{16}BrF_3NO_3$ requires 454.0260).

Example 507



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid

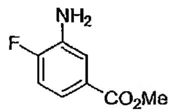
Step 1 Preparation of methyl 4-fluoro-3-nitrobenzoate



A 1 L 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 4-fluoro-3-nitrobenzoic acid (50 g, 0.27 mol) and methanol (300 mL). The system was cooled to 0 C and acetyl choride (27 mL, 0.37 mol) was added dropwise. The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 1.5 h. The reaction mixture was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to give methyl 4-fluoro-3-nitrobenzoate as an orange solid (40.6 g, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.67 ((dd, J = 2.2 and 6.8 Hz, 1H), 8.34 (dddd, J

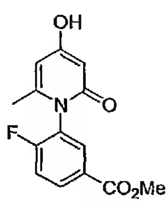
= 2.2, 4.4, 6.4 and 8.8 Hz, 1H), 7.55 (dd, J = 8.8 and 10.8 Hz, 1H), 3.94 (s, 3H) ppm. ES-HRMS m/z 200.02446 (M+H calcd for $C_8H_7FNO_4$ requires 200.0354).

Step 2 Preparation of methyl 3-amino-4-fluorobenzoate



A Parr bottle was charged with the product of Step 1 (40 g, 0.2 mol), ethanol (400 mL) and10% Pd/C (1 g g). The system was flushed twice with nitrogen and hydrogen. The reaction mixture was hydrogenated at 40 psi until no starting material was visible by LC-MS. The reaction mixture was slurried with Celite and then was filtered through a pad of celite. The filtrate and ensuing ethanol washes were concentrated in vacuo to give methyl 3-amino-4-fluorobenzoate as an orange solid (30.6 g, 91%). ^1H NMR (400 MHz, CD_3OD) δ 7.54 (d, J = 8.7 Hz, 1H), 7.35 (m, 1H), 7.06 (t, J = 8.7 Hz, 1H), 3.09 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -131.02 (1F) ppm. ES-HRMS m/z 199.0281 (M+H calcd for $C_8H_7FNO_4$ requires 199.02).

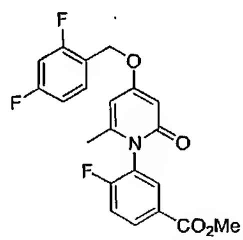
Step 3 Preparation of methyl 4-fluoro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate



A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 3 (30 g, 0.18 mol), 4-hydroxy-6-methyl-2-pyrone (22.6 g, 0.18 mol), and o-dichlorobenzene (90 mL). The

system was immersed in a 170 C oil bath for 30 minutes and was then cooled to room temperature. The reaction mixture was washed with aqueous Na_2CO_3 (38 g, 0.36 mol, 300 mL water). The aqueous layer was washed with ethyl acetate and then was acidified to pH 1-2 with concentrated HCl. This was extracted with ethyl acetate, which was then dried with $MgSO_4$ and concentrated in vacuo. The viscous orange oil was used without further purification (14.4 g, 28%). ^1H NMR (400 MHz, CD_3OD) δ 8.18 (dddd, J = 2.3, 5.2, 7.2 and 8.8 Hz, 1H), 7.97 (dd, J = 2 and 7.2 Hz, 1H), 7.44 (t, J = 8.8 Hz, 1H), 6.09 (d, J = 1.8 Hz, 1H), 5.78 (d, J = 2.4 Hz, 1H), 3.9 (s, 3H), 2.14 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -117.29 (1F) ppm. ES-HRMS m/z 278.0796 (M+H calcd for $C_{14}H_{13}FNO_4$ requires 278.0823).

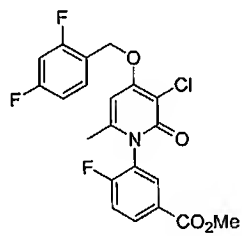
Step 4 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 3 (14.4 g, 51.9 mmol) and N,N-dimethyl formamide (40 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (10.9 mL, 72.8 mmol) was added followed by 2,4-difluorobenzyl bromide (9.3 mL, 72.8 mmol). The reaction mixture was stirred at 65 C for 18 h, was poured into saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to give the title product, as

an orange oil (21.5g), which was carried on to the next reaction without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (dddd, J = 2.2, 4.8, 7.2 and 8.8 Hz, 1H), 8.00 (dd, J = 2.2 and 7.2 Hz, 1H), 7.56 (td, J = 2.4, 6.4 and 9.2 Hz, 1H), 7.46 (t, J = 9.2 Hz, 1H), 7.02 (m, 2H), 6.18 (dd, J = 0.8 and 2.6 Hz, 1H), 6.04 (d, J = 2.7 Hz, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 1.98 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.34 (1F), -116.00 (1 F), -117.35 (1 F) ppm. ES-HRMS m/z 404.1104 (M+H calcd for $C_{21}H_{17}F_3NO_4$ requires 404.1104).

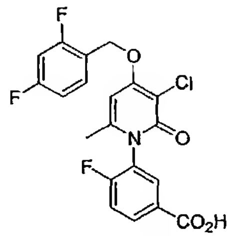
Step 5 Preparation of methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate



A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (21 g, 52 mmol) and N-methyl-2-pyrrolidine (100 mL). N-Chloro succinimide (8.3 g, 62 mmol) was added and the reaction mixture was stirred at 65 C for 2 h. The mixture was then cooled to room temperature, poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was triturated with diethyl ether and filtered to give the title compound, as a white powder (5.9 g, 25%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (dddd, J = 2, 4.8, 6.8 and 8.8 Hz, 1H), 8.03 (dd, J = 2 and 7.2 Hz, 1H), 7.62 (q, J = 8.4 and14.8 Hz, 1H), 7.48 (t, J = 14 Hz, 1H), 7.04 (m, 2H),

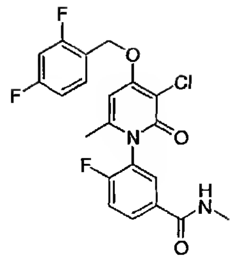
6.69 (s, 1H), 5.36 (s, 2H), 3.91 (s, 3H), 2.08 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.38 (1F), -115.97 (1 F), -117.43 (1 F) ppm. ES-HRMS m/z 438.0723 (M+H calcd for $C_{21}H_{16}ClF_3NO_4$ requires 438.0714).

Step 6 Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid



A 100 mL round bottomed flask was charged with the product of Step 5 (2.5 g, 5.72 mmol), tetrahydrofuran (40 mL), methanol (10 mL), and water (10 mL). To this slurry was added 2.5 N NaOH (4.6 mL, 11.4 mmol). The reaction mixture became clear after 5 minutes and the reaction was complete in 35 minutes by LC-MS. The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 3 with 6N HCl. The desired compound was precipitated by the addition of diethyl ether and subsequent filtration. The title compound was isolated as a white powder (2.5 g, 98%). ^{1}H NMR (400 MHz, dmso-d_6) δ 8.10 (dddd, J = 2.1, 4.8, 7.2 and 8.4 Hz, 1H), 8.00 (dd, J = 2.1 and 7.6 Hz, 1H), 7.66 (q, J = 9.2 and 15.6 Hz, 1H), 7.57 (t, J = 8.8 Hz, 1H), 7.34 (td, J = 2.4 and 10.4 Hz, 1H), 7.17 (tdd, J = 1, 2.7 and 8.4 Hz, 1H), 6.76 (s, 1H), 5.33 (s, 2H), 1.98 (s, 3H) ppm. ^{19}F NMR (400 MHz, dmso-d_6) δ -109.32 (1F), -113.64 (1 F), -117.22 (1 F) ppm. ES-HRMS m/z 424.0575 (M+H calcd for $C_{20}H_{14}ClF_3NO_4$ requires 424.0558).

Example 508



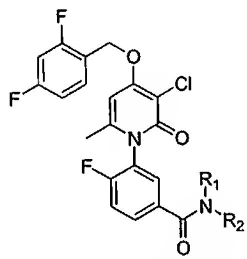
Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (0.300 g, 0.708 mmol) and 1-hydroxybenzotriazole (0.048 g, 0.45 mmol). N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1.2 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional N,N-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. N-Methyl amine (1 mL, 2 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.17 g of polyamine resin (2.63 mmol/g) and approximately 2.8 g of methylisocyanate functionalized polystyrene (1.5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble

byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial and the resulting solid was triturated with diethyl ether to give an off-white solid. (0.168 g, 59%)

^1H NMR (400 MHz, CD_3OD) δ 8.02 (dddd, J = 2, 4.4, 7.2 and 8.4 Hz, 1H), 7.80 (dd, J = 2 and 6.8 Hz, 1H), 7.62 (q, J = 8 and 14.4 Hz, 1H), 7.34 (t, J = 8.8 Hz, 1H), 7.04 (m, 2H), 6.69 (s, 1H), 5.36 (s, 2H), 3.29 (s, 3H), 1.98 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -108.94 (1F), -113.55 (1 F), -117.76 (1 F) ppm. ES-HRMS m/z 437.0861 (M+H calcd for $C_{21}H_{17}ClF_3N_2O_3$ requires 437.0874).

Examples 509-518 ,

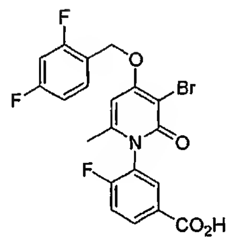


By following the method of Example 508 and replacing N-methylamine with the appropriate amine, the compounds of Examples 509-518 are prepared.

Example No.	R_1	R_2	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 509	CH_3	CH_3	59	$C_{22}H_{19}ClF_3N_2O_3$	451.1031	451.1016
Ex. 510	H	CH_2CH_2OH	70	$C_{22}H_{19}ClF_3N_2O_4$	467.0980	467.0985
Ex. 511	$CH_2CH_2N(CH_3)$-	$CH_2CH_2N(CH_3)$-	70	$C_{25}H_{24}ClF_3N_3O_3$	506.1453	506.1447
Ex. 512	CH_2CH_2O-	CH_2CH_2O-	19	$C_{24}H_{21}ClF_3N_2O_4$	493.1101	493.1136
Ex. 513	H	$CH_2CH_2OCH_3$	59	$C_{23}H_{21}ClF_3N_2O_4$	481.1136	481.1136

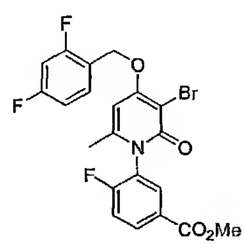
Ex. 514	CH_3	CH_2CH_2OH	63	$C_{23}H_{21}ClF_3N_2O_4$	481.1136	481.1131
Ex. 515	H	$CH_2CH_2CH_2OH$	51	$C_{23}H_{21}ClF_3N_2O_4$	481.1136	481.1121
Ex. 516	H	$CH_2CH(OH)CH_2OH$	64	$C_{23}H_{21}ClF_3N_2O_5$	497.1086	497.1102
Ex. 517	H	$C(CH_3)_2CH_2OH$-	54	$C_{24}H_{23}ClF_3N_2O_4$	495.1293	495.1303
Ex. 518	CH_2CH_2NH-	CH_2CH_2NH-	34	$C_{23}H_{22}ClF_3N_3O_3$	491.89	

Example 519



Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid

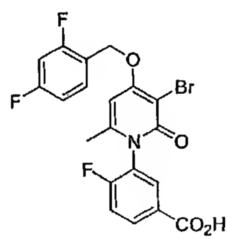
Step1 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-

fluorobenzoate (7.3 g, 18 mmol) and N-methyl-2-pyrrolidine (20 mL). N-Bromo succinimide (3.5 g, 19.8 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. The mixture poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was triturated with diethyl ether and filtered to give the title compound as a white powder (3.49 g). ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (qd, J = 3, 6.8 and 15.6 Hz, 1H), 7.84 (d, J = 2.12 Hz, 1H), 7.64 (q, J = 8.4 and14.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.04 (m, 2H), 6.60 (s, 1H), 5.34 (s, 2H), 3.87 (s, 3H), 2.00 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.51 (1F), -115.98 (1F), -117.43 (1F) ppm. ES-HRMS m/z 494.0387(M+H calcd for $C_{22}H_{19}BrF_2NO_5$ requires 494.0409).

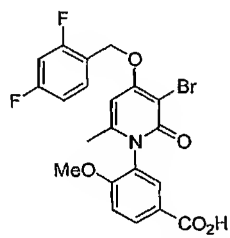
Step 2 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid



A 100 mL round bottomed flask was charged with the product of Step 2 (3.4 g, 7.05 mmol), tetrahydrofuran (40 mL), methanol (10 mL), and water (10 mL). To this slurry was added 2.5 N NaOH (5.6 mL, 14.1 mmol). The reaction mixture became clear after 5 minutes and the reaction was complete in 1 h by LC-MS. The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 1-2 with 6N HCl. The desired compound was precipitated by the addition of water and diethyl ether and subsequent filtration. The title

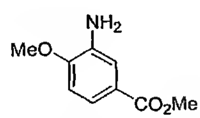
compound was isolated as a white powder (2.64 g, 80%). ^1H NMR (400 MHz, CD_3OD) δ 8.21 (dddd, J = 2.4, 5.2, 7.2 and 9.2 Hz, 1H), 8.00 (dd, J = 2.0 and 7.2 Hz, 1H), 7.65 (q, J = 8.4 and 14.8 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.04 (appt, J = 9.6 Hz, 1H), 6.65 (s, 1H), 5.36 (s, 2H), 2.07 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.40 (1F), -116.00 (1 F), -118.36 (1 F) ppm. ES-HRMS m/z 480.0259 (M+H calcd for $C_{21}H_{17}BrF_2NO_5$ requires 480.0253).

Example 520



Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoic acid

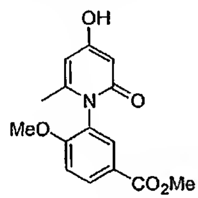
Step 1 Preparation of methyl 3-amino-4-methoxybenzoate



A 1 L 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 3-amino-4-methoxy benzoic acid (50 g, 0.299 mol) and methanol (300 mL). The system was cooled to 0 C and acetyl choride (30 mL, 0.42 mol) was added dropwise. The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 1.5 h. The reaction mixture was cooled to room temperature,

quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to give methyl 3-amino-4-methoxybenzoate as a dark solid (47.9 g, 88%). ^1H NMR (400 MHz, CD_3OD) δ 7.40 (t, J = 2 68 Hz, 1H), 7.37 (t, J = 2.0 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 3.98 (s, 3H), 3.81 (s, 3H) ppm. ES-HRMS m/z 182.0826 (M+H calcd for $C_9H_{12}ClNO_3$ requires 182.0812).

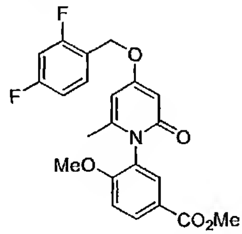
Step 2 Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methoxybenzoate



A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 1 (23.5 g, 0.129 mol), 4-hydroxy-6-methyl-2-pyrone (17.8 g, 0.14 mol), and o-dichlorobenzene (200 mL). The system was immersed in a 170 C oil bath for 2 h and was then cooled to room temperature. The reaction mixture was washed with aqueous Na_2CO_3 (28 g, 0.26 mol, 500 mL water). The aqueous layer was washed with ethyl acetate and then was acidified to pH 1-2 with concentrated HCl. This was extracted with ethyl acetate, which was then dried with Na_2SO_4 and concentrated in vacuo. The viscous orange oil was triturated with MeOH to give the title compound as a yellow solid (1.61 g, 4%). ^1H NMR (400 MHz, CD_3OD) δ 8.14 (dd, J = 2.2 and 8.8 Hz, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 6.05 (d, J = 2.3 Hz, 1H), 5.77 (d, J = 2.3 Hz, 1H), 3.88 (s,

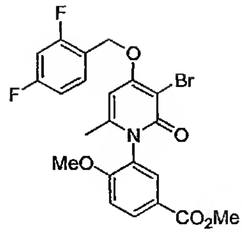
3H), 3.87 (s, 3H), 1.90 (s, 3H) ppm. ES-HRMS m/z 290.0997 (M+H calcd for $C_{15}H_{16}NO_5$ requires 290.1023).

Step 3 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoate



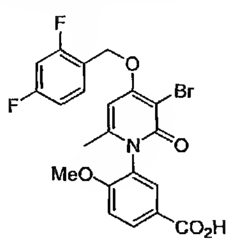
A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 2 (1.6 g, 5.5 mmol) and N,N-dimethyl formamide (10 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (0.91 mL, 6 mmol) was added followed by 2,4-difluorobenzyl bromide (0.77 mL, 6 mmol). The reaction mixture was stirred at 60 C for 4 h, was poured into saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to give the title compound as an orange foam (2.13g, 93%), which was carried on to the next reaction without further purification. ^1H NMR (400 MHz, CD_3OD) δ 8.17 (dd, J = 2.64 and 11.6 Hz, 1H), 7.82 (td, J = 2.7 and 6.8 Hz, 1H), 7.57 (m, 1H), 7.29 (d, J = 11.6 Hz, 1H), 7.02 (m, 2H), 6.16 (m, 1H), 6.03 (d, J = 3.5 Hz, 1H), 5.14 (s, 2H), 3.89 (s, 6H), 1.93 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.43(1F), -116.04 (1 F) ppm. ES-HRMS m/z 416.1310 (M+H calcd for $C_{22}H_{20}F_2NO_5$ requires 416.1304).

Step 4 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoate



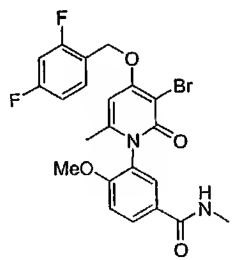
A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 3 (2.1 g, 5.06 mmol) and N-methyl-2-pyrrolidine (10 mL). N-Bromo succinimide (1 g, 5.56 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The mixture poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica (1:1 hexanes: ethyl acetate) to give the title compound as an orange oil (0.77 g, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (app qd, J = 2.5 and 7.2 Hz, 1H), 7.84 (d, J = 2.6 Hz, 1H), 7.64 (m, 1H), 7.30 (d, J = 9.2 Hz, 1H), 7.04 (appt, J = 8.4 Hz, 2H), 6.60 (s, 1H), 5.33 (s, 2H), 3.80 (s, 6H), 1.99 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.56 (1F), -116.00 (1 F) ppm. ES-HRMS m/z 494.0398 (M+H calcd for $C_{22}H_{19}BrF_2NO_5$ requires 494.0409).

Step 5 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoic acid



A 100 mL round bottomed flask was charged with the product of Step 4 (0.77 g, 1.55 mmol), tetrahydrofuran (10 mL), methanol (5 mL), and water (5 mL). To this slurry was added 2.5 N NaOH (1.2 mL, 3.1 mmol). The reaction mixture became clear after 30 minutes and the reaction was complete in 1 h by LC-MS. The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 2-3 with 6N HCl. The desired compound was precipitated by the addition of water and diethyl ether and subsequent filtration. The title compound was isolated as a white powder (0.60 g, 81%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (dd, J = 2.2 and 8.8 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.64 (q, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.34 (t, J = 8.8 Hz, 2H), 6.60 (s, 1H), 5.34 (s, 2H), 3.87 (s, 3H), 2.01 (s, 3H) ppm. ES-HRMS m/z 480.0259 (M+H calcd for $C_{21}H_{17}BrF_2NO_5$ requires 480.0253).

Example 521



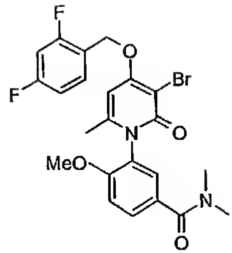
Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxy-N-methylbenzamide

Step 1

To a reaction vessel (borosilicate culture tube) was added Example 520 (0.300 g, 0.624 mmol) and 1-hydroxybenzotriazole (0.042 g, 0.31 mmol). N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1.06 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional

N,N-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. N-Methyl amine (2 mL, 4 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 g of polyamine resin (2.63 mmol/g) and approximately 2.5 g of methylisocyanate functionalized polystyrene (1.5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N_2 over the vial and the resulting solid was triturated with diethyl ether to give the desired product as an off-white solid (0.094 g, 31%). ^1H NMR (400 MHz, CD_3OD) δ 7.98 (dd, J = 2.2 and 8.8 Hz, 1H), 7.64 (m, 2H), 7.28 (d, J = 9.2 Hz, 1H), 7.04 (t, J = 9.2 Hz, 2H), 6.60 (s, 1H), 5.34 (s, 2H), 3.86 (s, 3H), 2.88 (s, 3H), 2.01 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.59 (1F), -116.01 (1 F) ppm. ES-HRMS m/z 493.0593 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493.0569).

Example 522

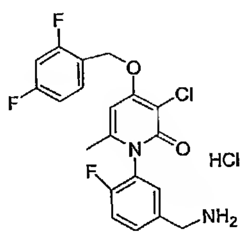


Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxy-N,N-dimethylbenzamide

The title compound was prepared essentially as in Example 521. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (m, 1H), 7.61 (dd, J = 2 and 8.8 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.04 (t, J = 8 Hz, 2H), 6.59 (s, 1H), 5.33 (s, 2H), 3.85 (s, 3H), 3.07 (s, 6H), 2.02 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.60 (1F), -116.01 (1 F) ppm. ES-HRMS m/z 507.0716 (M+H calcd for $C_{23}H_{22}BrF_2N_2O_4$ requires 507.0726).

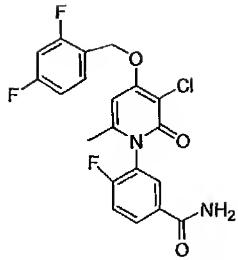
Example 523

1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



Step 1

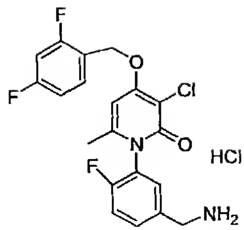
Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzamide



A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (2.58g, 6.1 mmol), 4-methylmorpholine (2.0 mL, 18.3 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.28g, 7.3 mmol) and tetrahydrofuran (30 mL). After stirring the mixture for 30 min at 25° C, NH_4OH (15.0 mL) was added. The mixture was stirred for 30 min and diluted with water. The product precipitated from solution. The precipitated was filtered and washed with water and diethyl ether to give the title compound (2.55g, 78%) as a white solid. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.10 (m, 1H), 7.9 (dd, J = 2.1 and 5.2 Hz, 1H), 7.65 (q, 6.7 and 8.5 Hz, 1H), 7.56 (t, J = 9.1 Hz, 1H), 7.35 (td, J = 2.4 and 8.2 Hz, 1H) 7.17 (td, J = 2 and 6.6 Hz, 1H) 6.78 (s, 1H), 5.36 (s, 2H), 2 (s, 3H) ppm. ES-HRMS m/z 423. 0719 (M+H calcd for $C_{20}H_{15}ClF_3N_2O_3$ requires 423.0718).

Step 2

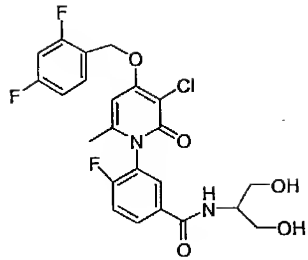
Preparation of 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product from step 1 (1.5 g, 3.5 mmol), BH_3•THF complex (7.4 mL, 7.4 mmol), and tetrahydrofuran (15 mL). The mixture was refluxed for 6 h, allowed to cool to room temperature and quenched with HCl 6N. The organics were evaporated and the remaining aqueous solution was saturated with NaOH 2.5N and extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. HCl 6N was added, and concentrated in vacuo. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.2 (m, 1H), 7.6 (m, 1H), 7.5 (m, 1H), 7.3 (t, J = 9.8 Hz, 1H), 7.16 (t, J = 8.6 Hz, 1H) 6.78 (s, 1H), 5.36 (s, 2H), 4.05 (d, J = 5.8 Hz, 2H), 2 (s, 3H) ppm. ES-HRMS m/z 409. 0940 (M+H calcd for $C_{20}H_{17}ClF_3N_2O_2$ requires 409.0925).

Example 524

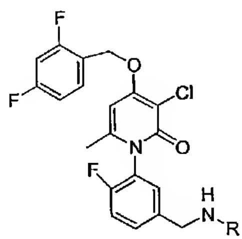
3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide

The title compound was prepared essentially as in Example 521. ^{1}H NMR (400 MHz, CD_3OD) δ 8.1 (m, 1H), 7.8 (dd, J = 2.3 and 5.1 Hz, 1H), 7.6 (q, J = 7.4 and 7.0 Hz, 1H), 7.41 (t, J = 8.9 Hz, 1H), 7.04 (m, 2H) 6.7 (s, 1H), 5.36 (s, 2H), 4.1 (t, J = 5.8 Hz, 1H), 3.7 (d, J = 5.1 Hz, 4H) 2.1 (s, 3H) ppm. ES-HRMS m/z 497. 1045 (M+H calcd for $C_{23}H_{21}ClF_3N_2O_5$ requires 497.1086).

Examples 525-528



The compounds of Examples 525-528 are prepared by derivitazion of Example 523. The analytical data are shown below.

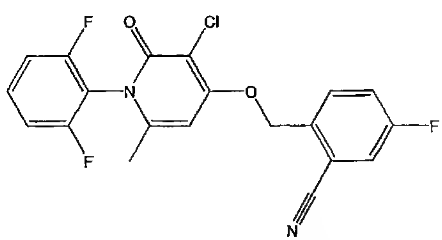
Ex. No.	R	MF	M+H	ESHRMS

			Requires	m/z
Ex. 525	-C(O)CH_3	$C_{22}H_{18}ClF_3N_2O_3$	451.1031	451.1010
Ex. 526	-C(O)CH_2OCH_3	$C_{23}H_{20}ClF_3N_2O_4$	481.1136	481.1132
Ex. 527	-SO_2CH_3	$C_{21}H_{18}ClF_3N_2O_4S$	487.0701	487.0679
Ex. 528	-C(O)NH_2	$C_{21}H_{16}ClF_3N_3O_3$	452.0983	452.0987

NMR characterization of compounds of Examples 525-528

Ex.No.	NMR Data
525	^{1}H NMR (400 MHz, CD_3OD) δ 7.6 (q, J = 7.8 and 7.0 Hz, 1H), 7.5 (m, 1H), 7.3 (t, J = 9.0 Hz, 1H), 7.2 (dd, J = 1.9 and 5.1 Hz, 1H), 7.05 (m, 2H), 6.65 (s, 1H), 5.36 (s, 2H), 4.39 (s, 2H), 2.1 (s, 3H), 1.98 (s, 3H) ppm
526	^{1}H NMR (400 MHz, CD_3Cl_3) δ 7.45 (q, J = 8.6 and 6.2 Hz, 1H), 7.3 (m, 1H), 7.1 (m, 2H), 6.85 (q, J = 6.5 and 1.9 Hz, 1H), 6.78 (td, J = 2.7 and 7.8 Hz, 1H), 6.2 (s, 1H), 5.2 (s, 2H), 4.39 (d, J = 6.2 Hz, 2H), 4.0 (s, 3H) 2.3 (s, 2H), 2.0 (s, 3H), 1.98 (s, 3H) ppm
527	^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (q, J = 8.2 and 6.3 Hz, 1H), 7.33 (m, 1H), 7.23(m, 1H), 7.1 (t, J = 8.9, 1H), 6.9 (td, J = 0.78 and 6.6 1H), 6.8 (td, J = 2.7 and 6.25 Hz, 1H), 6.2 (s, 1H), 5.2 (s, 2H), 4.2 (s, 2H), 2.8 (s, 3H) 2.0 (s, 3H) ppm
528	^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.61 (q, J = 8.9 and 6.6 Hz, 1H), 7.38(d, J = 7.8 Hz, 1H), 7.3 (d, J = 10.2 Hz, 1H) 7.21 (d, J = 7.4 Hz, 1H), 7.1 (t, J = 8.6 Hz, 1H), 6.71 (s, 1H), 6.5 (t, J = 5.8 Hz, 1H), 5.56 (s, 2H), 5.3 (s, 2H), 4.18 (d, J = 6.25 Hz, 2H), 3.61 (s, 1H), 1.98 (s, 3H) ppm

Example 529

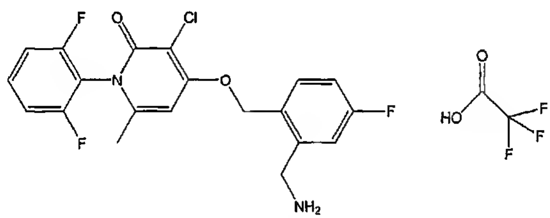


2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile

2-(bromomethyl)-5-fluorobenzonitrile (3.47 g, 16.2 mmol), 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (3.15 g, 11.6 mmol), K_2CO_3 (2.56 g, 18.6 mmol), and 18-crown-6 (0.15 g) were dissolved in N,N-dimethylacetamide (25 mL). Reaction mixture stirred on 60°C oil bath for 4 hours. Solvent removed by distillation. Reaction neutralized with 5% citric acid. The solid product was washed with hexane followed by 30% EtOAc/hexane. Filtered a brown solid (5.2 g, 79% yield).

^1H NMR (CD_3OD / 400MHz) δ7.82 (m, 2H), 7.61 (m, 4H), 6.75 (s, 1H), 5.49 (s, 2H), 2.13 (s, 3H). ESHRMS m/z 405.0616 (M+H $C_{20}H_{13}ClF_3N_2O_2$ requires 405.0612).

Example 530

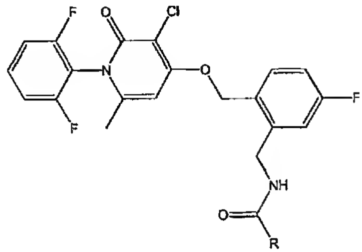


4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

BH_3THF (17.8 mL, 17.8 mmol) was added dropwise to a chilled (0°C) solution of 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile (3.61 g, 8.92 mmol) in THF (30 mL). Following the addition, the reaction was heated at 60°C for 1.5 hours. The reaction was quenched with MeOH, the solvent evaporated, and the crude product purified by prep HPLC. The product was isolated by freeze-drying and evaporation of the solvent to give a white solid (1.52 g, 32.6%). ^1H NMR (CD_3OD/

400MHz) δ7.62 (m, 2H), 7.32 (m, 1H), 7.25 (tr, 2H, J = 8.00 Hz), 7.18 (m, 1H), 6.78 (s, 1H), 5.43 (s, 1H), 4.22 (s, 1H), 2.14 (s, 3H). ESHRMS m/z 409.0900 (M+H $C_{20}H_{17}N_2O_2F_3Cl$ requires 409.0925).

Examples 531-551



The compounds of Examples 531-551 are prepared by derivitazion of Example 530. The analytical data are shown below.

Compound No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 531	$-OCH_3$	$C_{22}H_{18}ClF_3N_2O_4$	467.0980	467.0985
Ex. 532	$-CF_3$	$C_{22}H_{15}ClF_6N_2O_3$	505.0748	505.0754
Ex. 533	-O-isopropyl	$C_{24}H_{22}ClF_3N_2O_4$	495.1293	495.1304
Ex. 534	$-NH-CH_2CH_3$	$C_{23}H_{21}ClF_3N_3O_3$	480.1296	480.1277
Ex. 535	-O-tetrahydrofuran-3-yl	$C_{25}H_{22}ClF_3N_2O_5$	523.1242	523.1282
Ex. 536	-O-propyl	$C_{24}H_{22}ClF_3N_2O_4$	495.1293	495.1338
Ex. 537	$-O-CH_2CH=CH_2$	$C_{24}H_{20}ClF_3N_2O_4$	493.1136	493.1116
Ex. 538	$-O-CH_2C\equiv CH$	$C_{24}H_{18}ClF_3N_2O_4$	491.0980	491.0961
Ex. 539	-O-tButyl	$C_{25}H_{24}ClF_3N_2O_4$	509.1449	509.1436
Ex. 540	-NH-tButyl	$C_{25}H_{25}ClF_3N_3O_3$	508.1609	508.1574
EX. 541	$-SO_2CH_2CH_2CH_3$	$C_{23}H_{22}ClF_3N_2O_4S$	515.1014	515.0979

Ex. 542	$-SO_2CH_2CH_3$			
Ex. 543	-NH-isopropyl	$C_{24}H_{23}ClF_3N_3O_3$	494.1453	494.1456
Ex. 544	$-CH_2OCH_3$	$C_{23}H_{20}ClF_3N_2O_4$	481.1136	481.1174
Ex. 545	$-NHCH_3$	$C_{22}H_{20}ClF_3N_3O_3$	466.1140	466.1141
Ex. 546	$-N(CH_3)$(tButyl)	$C_{26}H_{27}ClF_3N_3O_3$	522.1766	522.1737
Ex. 547	-NH(cyclopropyl)	$C_{24}H_{21}ClF_3N_3O_3$	492.1296	492.1285
Ex. 548	$-NHCH_2CF_3$	$C_{23}H_{17}ClF_6N_3O_3$	534.1014	534.1005
Ex. 549	$NHCH_2$(cyclopropyl)	$C_{25}H_{23}ClF_3N_3O_3$	506.1453	506.1432
Ex. 550	$-NHCH_2$(tButyl)	$C_{26}H_{27}ClF_3N_3O_3$	522.1766	522.1740
Ex. 551	$-N(CH_3)_2$	$C_{23}H_{22}ClF_3N_3O_3$	480.1296	480.1307

NMR characterization of compounds of Examples 531-551

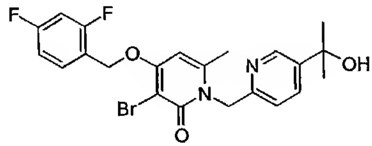
Ex. No.	NMR data
531	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 8.00Hz), 7.14 (m, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 5.40 (s, 2H), 4.42 (s, 2H), 3.63 (s, 3H), 2.12 (s, 3H)
532	^{1}H NMR (CD_3OD / 400MHz) δ7.59 (m, 2H), 7.24 (t, 2H, J = 8.00 Hz), 7.11 (m, 2H), 6.73 (s, 1H), 5.43 (s, 2H), 4.62 (s, 2H), 2.12 (s, 3H)
533	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 7.60 Hz), 7.13 (m, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 5.40 (s, 2H), 4.81 (m, 1H), 4.41 (s, 2H), 2.12 (s, 3H), 1.21 (d, 6H, J = 6.00 Hz)
534	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 0.80 Hz), 7.13 (m, 1H), 7.03 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.44 (s, 2H), 3.12 (q, 2H, J = 7.20 Hz), 2.12 (s, 3H), 1.08 (t, 3H, J = 7.20 Hz)
535	^{1}H NMR (CD_3OD / 300MHz) δ7.62 (m, 1H), 7.54 (m, 1H), 7.25 (t, 2H, J = 8.4 Hz), 7.15 (m, 1H), 7.07 (m, 1H), 6.75 (s, 1H), 5.41 (s, 2H), 5.15 (s br, 1H), 4.44 (s, 2H), 3.82 (m, 4H), 2.13 (s, 4H), 2.03 (s br, 1H)
536	^{1}H NMR (CD_3OD / 300MHz) δ7.62 (m, 1H), 7.54 (m, 1H), 7.25 (t, 2H, J = 8.1 Hz), 7.15 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.43 (s, 2H), 3.98 (t, 2H, J = 6.6 Hz), 2.13 (s, 3H), 1.63 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz)
537	^{1}H NMR (CD_3OD / 300MHz) δ7.62 (m, 1H), 7.54 (m, 1H), 7.25 (t, 2H, J = 8.4 Hz), 7.14 (m, 1H), 7.07 (m, 1H), 6.74 (s, 1H), 5.92 (m br, 1H), 5.41 (s, 2H), 5.29 (d, 1H, J = 17.7 Hz), 5.17 (d, 1H, J = 10.5 Hz), 4.63 (s, 1H), 4.53 (d, 2H, J = 5.4 Hz), 4.44 (s, 2H), 2.13 (s, 3H)
538	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 7.6 Hz), 7.14 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.65 (d, 2H, J = 2.4 Hz), 4.44 (s, 2H), 2.86 (t, 1H, J =

	2.4 Hz), 2.12 (s, 3H)
539	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (tr, 2H, J = 8.40), 7.12 (m, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 5.39 (s, 2H), 4.36 (s, 2H), 2.12 (s, 3H), 1.43 (s, 9H)
540	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (tr, 2H, J = 8.00 Hz), 7.12 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.37 (s, 2H), 4.39 (s, 2H), 2.12 (s, 3H), 1.28 (s, 9H)
541	^{1}H NMR (CD_3OD / 300MHz) δ7.59 (m, 2H), 7.26 (m, 3H), 7.11 (m, 1H), 6.75 (s, 1H), 5.46 (s, 2H), 4.40 (s, 2H), 3.02 (m, 2H), 2.12 (s, 3H), 1.80 (m, 2H), 1.03 (tr, 3H, J = 7.50 MHz)
542	^{1}H NMR (CD_3OD / 400MHz) δ7.58 (m, 2H), 7.26 (m, 3H), 7.10 (m, 1H), 6.74 (s, 1H), 5.45 (s, 2H), 4.39 (s, 2H), 3.06 (q, 2H, J = 7.60 Hz), 2.11 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz)
543	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 8.40 Hz), 7.12 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.44 (s, 2H), 3.77 (m, 1H), 2.12 (s, 3H), 1.10 (d, 6H, J = 6.40 Hz)
544	^{1}H NMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.54 (m, 1H), 7.24 (t, 2H, J = 7.6 Hz), 7.15 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.43 (s, 2H), 4.55 (s, 2H), 3.92 (s, 2H), 3.40 (s, 3H), 2.12 (s, 3H)
545	^{1}H NMR (CD_3OD / 300MHz) δ7.63 (m, 1H), 7.54 (m, 1H), 7.26 (t, 2H, J = 8.7 Hz), 7.15 (m, 1H), 7.05 (m, 1H), 6.75 (s, 1H), 5.42 (s, 2H), 4.47 (s, 2H), 2.70 (s, 3H), 2.14 (s, 3H)
546	^{1}H NNMR (CD_3OD / 300MHz) δ7.63 (m, 1H), 7.53 (m, 1H), 7.25 (t, 2H, J = 9.0 Hz), 7.14 (m, 1H), 7.04 (m, 1H), 6.76 (s, 1H), 5.41 (s, 2H), 4.44 (s, 2H), 2.90 (s, 3H), 2.13 (s, 3H), 1.39 (s, 9H)
547	^{1}H NNMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 7.6 Hz), 7.14 (m, 1H), 7.03 (m, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.47 (s, 2H), 2.46 (m, 1H), 2.12 (s, 3H), 0.68 (q, 2H, J = 5.2 Hz), 0.46 (m, 2H)
548	^{1}H NNMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 8.0 Hz), 7.12 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.47 (s, 2H), 3.79 (q, 2H, J = 9.6 Hz), 2.12 (s, 3H)
549	^{1}H NNMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 8.4 Hz), 7.14 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.45 (s, 2H), 2.96 (d, 2H, J = 6.8 Hz), 2.12 (s, 3H), 0.93 (m, 1H), 0.44 (m, 2H), 0.16 (q, 2H, J = 4.8 Hz)
550	^{1}H NNMR (CD_3OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 8.0 Hz), 7.14 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.46 (s, 2H), 2.92 (d, 2H, J = 4.8 Hz), 2.12 (s, 3H), 0.87 (s, 9H)
551	^{1}H NNMR (CD_3OD / 300MHz) δ7.62 (m, 1H), 7.52 (m, 1H), 7.25 (t, 2H, J = 8.7 Hz), 7.15 (m, 1H), 7.04 (m, 1H), 6.75 (s, 1H), 5.42 (s, 2H), 4.48 (s, 2H), 2.90 (s, 6H), 2.14 (s, 3H)

^{1}H NMR (CD_3OD / 400MHz) δ7.58 (m, 2H), 7.26 (m, 3H), 7.10 (m, 1H), 6.74 (s, 1H), 5.45 (s, 2H), 4.39 (s, 2H), 3.06 (q, 2H, J = 7.60 Hz), 2.11 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz)^{1}H NMR (CD_3OD / 300MHz) δ7.63 (m, 1H), 7.54 (m, 1H), 7.26 (t, 2H, J =

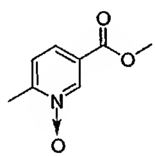
8.7 Hz), 7.15 (m, 1H), 7.05 (m, 1H), 6.75 (s, 1H), 5.42 (s, 2H), 4.47 (s, 2H), 2.70 (s, 3H), 2.14 (s, 3H). ESHRMS m/z 466.1141 (M+H $C_{22}H_{20}ClF_3N_3O_3$ requires 466.1140).

Example 552



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

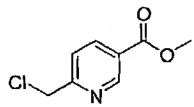
Step 1: Preparation of methyl 6-methylnicotinate 1-oxide.



Methyl 6-methylnicotinate (6.0 g, 39.7 mmol) was added into dichloromethane (100 mL) in the round bottom flask under nitrogen. 3-chloroperoxybenzoic acid (10.0 g, 57.9 mmol) was then added into the flask and stirred for 5 hour. Saturated sodium bicarbonate solution (100 ml) was added into the reaction and the mixture was transferred to separatory funnel. Additional 200mL of dichloromethane was added into the funnel and obtained the organic layer. The organic layer was washed with water (150 mL) and dried over anhydrous magnesium sulfate. The resulting solution was evaporated to yield white solid (6 g, 90 %). LC/MS, t_r = 0.33 minutes (5 to 95%

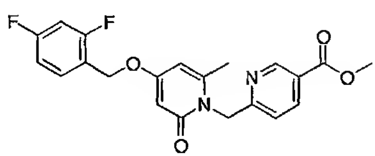
acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 168 (M+H). ES-HRMS m/z 168.0628 (M+H calcd for $C_8H_{10}NO_3$ requires 168.0655).

Step 2: Preparation of methyl 6-(chloromethyl)nicotinate .



Methyl 6-methylnicotinate 1-oxide (from Step 1) (6.0 g, 35.9 mmol) was was added into the p-toluenesulfonyl chloride (10 g, 52.4 mmol) in 100 mL of 1,4- dioxane. The mixture was heated to reflux for 20 hours. Saturated sodium bicarbonate solution (200 ml) was added into the reaction and the mixture was transferred to separatory funnel. The compound was extracted using ethyl acetate (300ml x 2) and the combined ethyl acetate solution was dried over magnesium sulfate and evaporated to black solid (5.2 g, 78%). LC/MS, t_r = 1.52 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 186 (M+H). ES-HRMS m/z 186.0314 (M+H calcd for $C_8H_9ClNO_2$ requires 186.0316).

Step 3: Preparation of methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate .



Methyl 6-(chloromethyl)nicotinate (from step 2). (2 g, 10.8 mmol) was added into 4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one in 20 mL of dimethyl formamide followed by addition of cesium carbonate (5g, 15.3 mmol). The

mixture was heated to 100 C for 20 hours. It was cooled to room temperature and added 400 mL of water. Brown precipitate came out of from solution. It was filtered and rinsed with water (200 mL x 3) and dried to obtain 4 g of solid. The product was purified using a Gilson Reversed Phase preparative chromatography to obtain white solid (1.4 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J =1.48 Hz, 1H), 8.19 (dd, J = 6.04, 2.15 Hz, 1H), 7.37 (app q, J = 8.32 Hz, 1H), 7.25 (d, J = 8.33 Hz, 1H), 6.84 (m, 2H), 5.94 (d, J = 2.82Hz, 1H), 5.83 (d, J = 2.15Hz, 1H), 5.36 (s, 2H), 4.97 (s, 2H), 3.90 (s, 3H), 2.27(s, 3H); LC/MS, t_r = 2.30 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 401 (M+H). ES-HRMS m/z 401.1307 (M+H calcd for $C_{21}H_{19}F_2N_2O_4$ requires 401.1307).

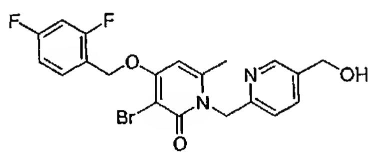
Step 4: Preparation of the title compound .

3 molar solution of methyl magnesium bromide in ether (5mL, 15mmol) was added into 5 ml of anhydrous tetrahydrofuran in the round bottom flaks under nitrogen. The mixture was cooled to 0°C. Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (from Step 3) (300mg, 0.75mmol)was dissolved in 5 ml of anhydrous tetrahydrofuran in dropper funnel and the solution was slowly added into cold methyl magnesium bromide solution in the round bottom flask. After the addition, the mixture was continue stirring at 0 C for 30 minute and cold solution of saturated ammonium chloride (100 ml) was added slowly into the reaction mixture. The mixture was transferred to separatory funnel and the product was extracted with ethyl acetate (200ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. The resulting residue (220 mg) was added into 10 ml of dichloromethane

followed by addition of N-bromo succinimide (100 mg, 0.56 mmol). The solution was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution (100 ml) was added into the reaction mixture and it was transferred to separatory funnel. The product was extracted with ethyl acetate (200ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness.

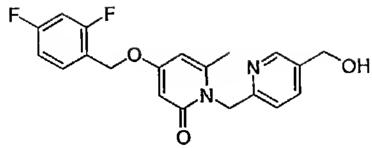
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J =1.88 Hz, 1H), 7.73 (dd, J = 5.77, 2.42 Hz, 1H), 7.55 (app q, J = 6.31 Hz, 1H), 7.30 (d, J = 8.19b Hz, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 6.00 (s, 1H), 5.37 (s, 2H), 5.19 (s, 2H), 2.48 (s, 3H), 1.56 (s, 6H); LC/MS, t_r = 2.29 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 479 (M+H). ES-HRMS m/z 479.0791 (M+H calcd for $C_{22}H_{22}BrF_2N_2O_3$ requires 479.0776).

Example 553



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

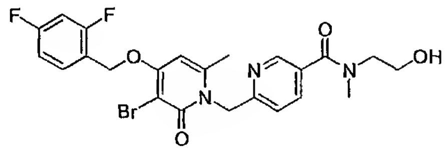


Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (from preparation of step 3) (350 mg, 0.87 mmol) was added into anhydrous tetrahydrofuran (15 ml) and the solution was cooled to -78 C. Into the cold solution, was added lithium aluminum hydride (100 mg, 2.6 mmol). After the addition, the reaction mixture was warm to 0 C and continue stirring for one additional hour. Potassium hydrogen sulfate (1 N solution, 150 ml) was added slowly into the reaction mixture to quench the reaction. The resulting mixture was transferred to a separatory funnel and the product was extracted with ethyl acetate (200ml x 2). The combine ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. LC/MS, t_r = 1.88 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 373 (M+H)

Step 2: Preparation of the title compound . 4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one (from step 1). (230 mg, 0.62 mmol) was added into 10 ml of dichloromethane followed by addition of N-bromo succinimide (110 mg, 0.62 mmol). The solution was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution (100 ml) was added into the reaction mixture and it was transferred to a separatory funnel. The product was extracted with ethyl acetate (200ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (app s, 1H), 7.64 (dd, J = 5.77, 2.29

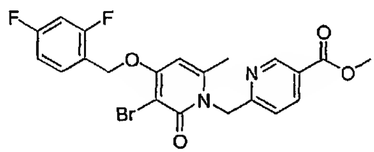
Hz, 1H), 7.55 (app q, J = 6.45 Hz, 1H), 7.33 (d, J = 6.05 Hz, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 6.00 (s, 1H), 5.39 (s, 2H), 5.19 (s, 2H), 4.68 (s, 2H), 2.46 (s, 3H); LC/MS, t_r = 2.01 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 451 (M+H)

Example 554



6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylnicotinamide

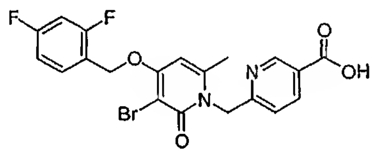
Step 1: Preparation of methyl 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate .



Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (350 mg, 0.87 mmol) (1.0 g, 2.5 mmol) was added into 150 ml of dichloromethane followed by addition of N-bromo succinimide (500 mg, 2.8 mmol). The solution was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution (300 ml) was added into the reaction mixture and it was transferred to a separatory funnel. The product was extracted with ethyl acetate (500ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (app d, J = 2.15 Hz, 1H), 8.21 (dd, J =

6.04, 2.15 Hz, 1H), 7.55 (app qt, J = 6.31 Hz, 1H), 7.41 (d, J = 6.31 Hz, 1H), 6.91 (m, 1H), 6.84 (m, 1H), 6.02 (s, 1H), 5.42 (s, 2H), 5.19 (s, 2H), 3.91 (s, 3H), 2.45 (s, 3H); LC/MS, t_r = 2.85 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 479 (M+H). ES-HRMS m/z 479.0415 (M+H calcd for $C_{21}H_{18}BrF_2N_2O_4$ requires 479.0413).

Step 2: Preparation of 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinic acid .



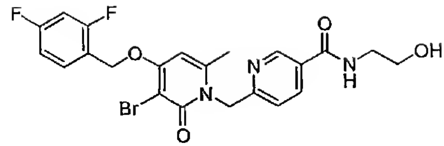
Methyl 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)- yl]methyl}nicotinate (from step 1) (1.0 g, 2.1 mmol) was added into the mixture of 100 ml tetrahydrofuran and 10 ml of methanol followed by addition of 2.5 N sodium hydroxide(0.85 ml, 2.1 mmol). The solution was heated to 50 C for 2 hours. After the solution was cooled to room temperature and evaporate to completely dried residue. The residue was added into 50 ml of tetrahydrofuran and 4 N HCl in 1,4-dioxane (0.52 ml, 2.1 mmol) and stirred the mixture for 30 minute. The mixture was evaporate to dryness. The residue was added 20 ml water and the aqueous solution was neutralized to exactly ph 7 by addition of saturated sodium bicarbonate solution drop wise. The resulting heterogeneous mixture was left standed for 20 hours. Filtered, rinsed with water (30 ml x 3) and dried over high vacuum oven to afford white solid(950 mg, 97%).

^1H NMR (400 MHz, $CDCl_3$ and CD_3OD) δ 8.98 (app br s, 1H), 8.15 (dd, J = 6.17, 2.02 Hz, 1H), 7.45 (app q, J = 6.58 Hz, 1H), 7.21 (d, J = 8.19 Hz, 1H), 6.84 (m, 1H), 6.76 (m, 1H), 6.04 (s, 1H), 5.35 (s, 2H), 5.12 (s, 2H), 2.32 (s, 3H); LC/MS, t_r = 2.48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 465 (M+H). ES-HRMS m/z 465.0254 (M+H calcd for $C_{20}H_{16}BrF_2N_2O_4$ requires 465.0256).

Step 3: Preparation of the title compound .

6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinic acid (from step 2)(230 mg, 0.5 mmol) was added into the 1-hydroxybenzotriazole (101mg, 0.75 mmol) in 5 ml of N,N-dimethylforamide. 4 -methyl morpholine (0.16 ml, 1.5 mmol) was added into the mixture followed by addition of 1-(3-(dimethylamino) propyl-3-ethylcarbodiimide hydrochloride (143 mg, 0.75 mmol). Stirred the mixture for 30 minute to become homogenous solution. To that homogenous solution, was added 2-(methylamino) ethanol(0.06 ml, 0.75 mmol) and the mixture was stirred for 20 hours. Water (150 ml) was added into the reaction mixture and the product was extracted using ethyl acetate (400ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^1H NMR (400 MHz, DMSO-d_6) δ 8.47 (app br s, 1H), 7.80 (br d, J = 7.92 Hz, 1H), 7.64 (app q, J = 6.58 Hz, 1H), 7.30 (m, 2H), 7.15 (m, 1H), 6.56 (s, 1H), 5.39 (s, 2H), 5.28 (s, 2H), 3.46 (m, 2H), 3.23 (m, 2H) 2.93 (m, 3H), 2.36 (s, 3H); LC/MS, t_r = 2.29 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 522.0850 (M+H calcd for $C_{23}H_{23}BrF_2N_3O_4$ requires 522.0835).

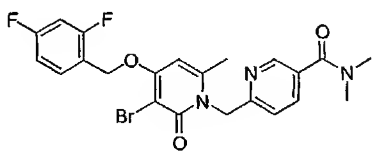
Example 555



6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)nicotinamide

Following the method of Example 554 (step 3) and substituting 2-(methylamino)ethanol for the ethanolamine obtained the title compound as a white solid (79% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.93 (d, J = 2.01 Hz, 1H), 8.21 (dd, J = 6.04, 2.21 Hz, 1H), 7.67 (app q, J = 6.44 Hz, 1H), 7.39 (d, J = 8.06 Hz, 1H), 7.08 (m, 2H), 6.58 (s, 1H), 5.55 (s, 2H), 5.35 (s, 2H), 3.74 (app t, J = 5.73Hz, 2H), 3.53 (app t, J = 5.73Hz, 2H), 2.49 (s, 3H); LC/MS, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 508.0673 (M+H calcd for $C_{22}H_{21}BrF_2N_3O_4$ requires 508.0678).

Example 556

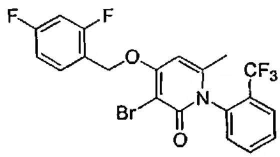


6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylnicotinamide

Following the method of Example 554 (step 3) and substituting dimethylamine for the ethanolamine obtained the title compound as a white solid (75% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 1.62 Hz, 1H), 7.68 (dd, J = 5.77, 2.15 Hz, 1H), 7.55

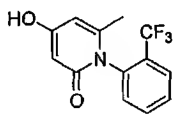
(app q, J = 6.45 Hz, 1H), 7.37 (d, J = 8.06 Hz, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 6.02(s, 1H), 5.40 (s, 2H), 5.20 (s, 2H), 3.09 (s, 3H), 2.97 (s, 3H), 2.45 (s, 3H); LC/MS, t_r = 2.45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 492.0710 (M+H calcd for $C_{22}H_{21}BrF_2N_3O_3$ requires 492.0729).

Example 557



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one

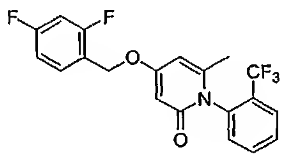
Step 1: Preparation of 4-hydroxy-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one .



4-hydroxy-6-methyl-2-pyrone (10g, 79.3 mmol) was added into the 2-(trifluoromethyl) aniline (14 ml, 111.3 mmol) in 10 ml of 1,2-dichlorobenzene in a round bottom flask. The mixture was then placed in a pre-heated oil bath at 165 C. After 30 minute of heating, the mixture was cooled to room temperature and added 250 ml of saturated sodium bicarbonate solution. The mixture was stirred at room temperature for 15 minutes and transferred to a separatory funnel. Ethyl acetate (300ml) was added into the separatory funnel and partitions the layers. The aqueous layer was obtained and the organic layer was added 200 ml of saturated sodium bicarbonate solution. The aqueous layer was obtained again and the

combined aqueous solution was neutralized with HCl solution. Upon neutralization, white solid precipitated out of the solution. Filtered the solid, rinsed with water (100 ml x5) and dried over high vacuum oven to obtain the white solid (7.5 g, 35.5%). LC/MS, t_r = 1.77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 270 (M+H).

Step 2: Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one .

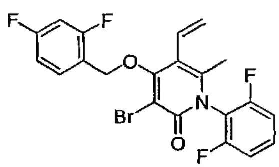


4-hydroxy-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one (from Step 1) (7.3 g, 27.1 mmol) was added into 3,4-difluorobenzyl bromide (5.5 g, 26.5 mmol) in 60 ml of dimethyl formamide. The mixture was cooled to 0 C and cesium carbonate (20g, 61.3 mmol) was added into the mixture. After the addition, the mixture was warmed to room temperature and stirred for 4 hours. Water (500ml) was added into the reaction mixture. Yellow solid came out of solution. Filtered and rinsed with water (200ml x 2) to obtain the yellow solid. Dissolved the solid in ethyl acetate (500 ml) and water (300 ml) and transfer to a separatory funnel and obtained the organic layer. The organic layer was washed again with water (200ml) and dried over anhydrous magnesium sulfate. The organic solution was evaporated to dryness. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J =7.65 Hz, 1H), 7.7 (t, J = 7.52 Hz, 1H), 7.58 (t, J = 7.65 Hz, 1H), 7.42 (q, J = 6.45 Hz,

1H), 7.27 (d, J = 7.78 Hz, 2H), 6.89 (m, 2H), 5.95 (app d, J = 2.42Hz, 1H), 5.90 (app d, J = 2.42Hz, 1H), 5.01 (app d, J = 2.94 Hz, 2H), 1.86 (s, 3H); LC/MS, t_r = 2.74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 396 (M+H)

Step 3: Preparation of the title compound.
N-bromosuccinimide (0.24g, 1.36 mmol) was added into 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one (0.54g, 1.36 mmol) in 20 ml of dichloromethane. The mixture was stirred at room temperature for 2 hours. Saturated sodium bicarbonate solution (150 ml) was added into the reaction mixture and the combine solution was transferred to a separatory funnel. The product was extracted with ethyl acetate (250ml). The ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J =7.25 Hz, 1H), 7.7 (app t, J = 7.66 Hz, 1H), 7.60 (m, 2H), 7.26 (s, 1H), 6.97 (m, 1H), 6.87 (m, 1H), 6.09 (s, 1H), 5.25 (app d, J = 3.35Hz, 2H), 1.94 (s, 3H); LC/MS, t_r = 2.84 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 474.0113 (M+H calcd for $C_{20}H_{14}BrF_5NO_2$ requires 474.0123).

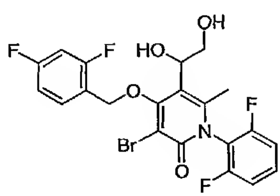
Example 558



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.00 g, 1.76 mmol) in anhydrous THF (12 mL) was added, sequentially, tributyl(vinyl)tin (1.21 g, 3.81 mmol) and tetrakis(triphenylphosphine)palladium (236 mg, 0.204 mmol) under an argon stream. The reaction vessel was then equipped with a reflux condenser and the reaction system purged with an argon flow. The resulting yellow solution was heated to 68 °C and stirred under a positive pressure of argon for 12.0 hours until complete disappearance of starting material by LCMS analysis. The reaction mixture was concentrated in vacuo and the resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a reddish solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (app q, J = 7.8 Hz, 1H), 7.45 (app tt, J = 8.4, 6.2, 1H), 7.09 (app t, J = 8.8 Hz, 2H), 6.90 (app t, J = 8.0 Hz, 1H), 6.83 (app dt, J = 6.8, 2.5 Hz, 1H), 6.51 (dd, J = 17.7, 11.4 Hz, 1H), 5.53 (dd, J = 11.4, 1.5 Hz, 1H), 5.41 (dd, J = 17.8, 1.5 Hz, 1H), 5.09 (br s, 2H), 2.09 (s, 3H); LC/MS C-18 column, t_r = 3.20 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 468 (M+H). ES-HRMS m/z 468.0210 (M+H calcd for $C_{21}H_{15}BrF_4NO_2$ requires 468.0217).

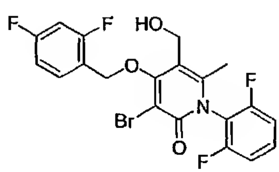
Example 560



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1H)-one

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one (0.970 g, 2.07 mmol) in water/acetone 1:3 (8.7 mL) was added, sequentially, osmium tetroxide (0.110 g, 0.433 mmol) and N-methyl morpholine oxide (1.32 g, 11.2 mmol). The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis, and the reaction was concentrated in vacuo. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (app q, J = 8.2 Hz, 1H), 7.45 (ddd, J = 14.7, 8.5, 6.8 Hz, 1H), 7.08 (app t, J = 8.5 Hz, 2H), 6.94 (app t, J = 8.2 Hz, 1H), 6.88 (app t, J = 8.5 Hz, 1H), 5.31 (AB-q, J = 10.6 Hz, Δ= 38.3 Hz, 2H), 5.07 (dd, J = 9.1, 3.8 Hz, 1H), 3.83 (t, J = 10.8 Hz, 1H), 3.60 (dd, J = 11.4, 3.9 Hz, 1H), 2.94 (br s, 1H), 2.16 (s, 3H); LC/MS C-18 column, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 502 (M+H). ES-HRMS m/z 502.0276 (M+H calcd for $C_{21}H_{17}BrF_4NO_4$ requires 502.0272).

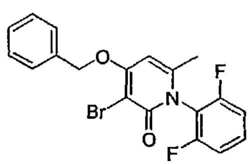
Example 561



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1H)-one

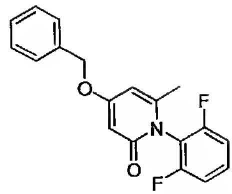
Step 1: To a -20 °C solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (0.659 g, 1.40 mmol) in methanol (10 mL) was added, portionwise, solid sodium borohyride (3.6 g, 96 mmol) over one hour until complete consumption of starting material by LCMS analysis. Next, the reaction mixture was diluted with 500 mL of ethyl acetate and washed with 3 X 200 mL of water. The resulting organic extract was Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 100 mL volume. The resulting liquid was diluted with hexanes (100 mL) to furnish an amorphous solid that was collected and dried at 1 mm Hg vacuum to furnish (620 mg, 94 %) of the desired product. ^1H NMR (400 MHz, d_4-MeOH) δ 7.70 (app q, J = 8.3 Hz, 1H), 7.62 (app tt, J = 10.4, 6.3 Hz, 1H), 7.25 (app t, J = 8.6 Hz, 2H), 7.03 (app t, J = 8.6 Hz, 1H), 6.88 (app t, J = 8.5 Hz, 1H), 5.31 (s, 2H), 4.58 (s, 2H), 2.17 (s, 3H); LC/MS C-18 column, t_r = 2.49 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 472 (M+H). ES-HRMS m/z 472.0152 (M+H calcd for $C_{20}H_{15}BrF_4NO_3$ requires 472.0166).

Example 562



4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-(benzyloxy)-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one .

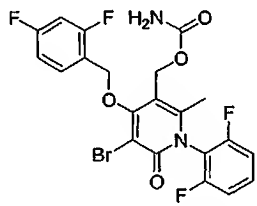


To a briskly stirred room temperature solution of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (1.43 g, 6.03 mmol) in dimethylformamide (4.6 mL) was added sequentially K_2CO_3 (2.01 g, 14.5 mmol) and benzyl bromide (2.40 mL, 20.2 mmol). The resulting suspension was stirred for 6.5 hours until complete consumption of starting material by LCMS analysis. The reaction was then diluted with ethyl acetate (200 mL) and brine washed (3 X 200 mL). The resulting organic extract was Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 100 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1.62 g, 82 %). ^1H NMR (300 MHz, d_4-MeOH) δ 7.62 (app tt, J = 8.6, 6.4 Hz, 1H), 7.52-7.32 (m, 4H), 7.30-7.12 (m, 3H), 6.27 (d, J = 1.6 Hz, 1H), 6.04 (d, J = 2.6 Hz, 1H), 5.18 (s, 2H), 2.06 (s, 3H). LC/MS C-18 column, t_r = 2.51 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 328 (M+H). ES-HRMS m/z 328.1179 (M+H calcd for $C_{19}H_{16}F_2NO_2$ requires 328.1144).

Step 2: To a room temperature solution of 4-(benzyloxy)-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (1.52 g, 4.64 mmol) in methylene chloride (15 mL) was added solid N-bromosuccinimide (2.01 g, 11.3 mmol) and the resulting reddish solution was stirred for 4.0 hours. At this time the reaction was diluted with ethyl acetate (400 mL) and washed with sodium sulfite (5 % aqueous solution, 100 mL) and brine

(3 X 200 mL). The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 60 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1.70 g, 91 %). ^1H NMR (300 MHz, d_4-MeOH) δ 7.64 (app tt, J = 8.6, 6.4 Hz, 1H), 7.57 (br d, J = 7.1 Hz, 1H), 7.50-7.34 (m, 4H), 7.27 (app t, J = 8.0 Hz, 1H), 7.26-7.21 (m, 1H), 6.66 (s, 1H), 5.40 (s, 2H), 2.12 (s, 3H); LC/MS C-18 column, t_r = 2.63 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 406 (M+H). ES-HRMS m/z 406.0228 (M+H calcd for $C_{19}H_{15}BrF_2NO_2$ requires 406.0249).

Example 563

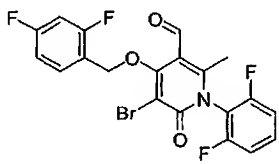


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl]methyl carbamate

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1H)-one (76.2 mg, 0.161mmol) in methylene chloride (0.4 mL) was added a solution of trichloroacetyl isocyanate (toluene, 0.60 M, 0.5 mL, 0.30 mmol). The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis. The reaction mixture was then directly applied to Al_2O_3 (0.5 g of Broeckman-activity type I) and the slurry was matured for three hours. At this time, the Al_2O_3 plug was flushed with ethyl acetate/methanol

(95:5) and the resulting mother liquor was concentrated to a residue that was subjected to SiO_2 chromatography using ethyl acetate/hexanes (1:1) to furnish a white solid (71.0 mg, 85 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.71-7.59 (m, 2H), 7.26 (app t, J = 8.5 Hz, 2H), 7.02 (app t, J = 9.2 Hz, 2H), 5.32 (s, 2H), 5.02 (s, 2H), 2.15 (s, 3H); LC/MS C-18 column, t_r = 2.35 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 515 (M+H). ES-HRMS m/z 515.0188 (M+H calcd for $C_{21}H_{16}BrF_4N_2O_4$ requires 515.0224).

Example 564

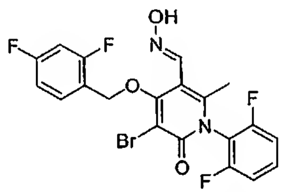


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)- 6-methylpyridin-2(1H)-one (550 mg, 1.10 mmol) in toluene (10.0 mL) was added lead(IV) acetate (810 mg, 1.82 mmol). The resulting dark brown solution was stirred for two hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 100 mL), and brine washed (3 X 300 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl

acetate/ hexanes (1:1) to furnish a light yellow solid (321 mg, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.56-7.48 (m, 2H), 7.12 (app t, J = 7.3 Hz, 2H), 6.94 (app t, J = 8.5 Hz, 1H), 6.88 (app t, J = 8.7 Hz, 1H), 5.33 (s, 2H), 2.45 (s, 3H); LC/MS C-18 column, t_r = 2.94 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 470 (M+H). ES-HRMS m/z 469.9996 (M+H calcd for $C_{20}H_{13}BrF_4NO_3$ requires 470.0009).

Example 565

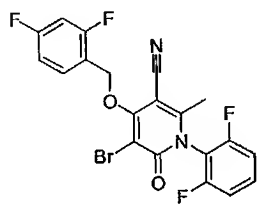


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime

Step 1: To a room temperature solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (316.5 mg, 0.673 mmol) in methanol (10.0 mL) was added solid $NH_2OH \bullet H_2O$(300.0 mg, 4.32 mmol) and sodium acetate (480.0 mg, 5.85 mmol). The resulting suspension was stirred for 1.5 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then concentrated in vacuo and the resulting residue was diluted with methylene chloride (300 mL) and water washed (2 X 100 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated to furnish a light yellow solid (390 mg, 99 %). ^{1}H NMR (400 MHz, d_4-MeOH with $CDCl_3$) δ 8.06 (s, 1H), 7.51-7.40 (m, 2H), 7.06 (app dd, J

= 8.6, 7.4 Hz, 2H), 6.88 (app dt, J = 8.3, 2.4 Hz, 1H), 6.83 (app dt, J = 9.2, 2.4 Hz, 1H), 5.13 (s, 2H), 2.76 (s, 3H); LC/MS C-18 column, t_r = 2.61 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 485 (M+H). ES-HRMS m/z 485.0093 (M+H calcd for $C_{20}H_{14}BrF_4N_2O_3$ requires 485.0118).

Example 566

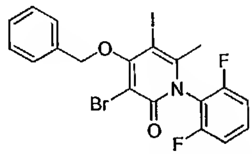


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile

Step 1: To a room temperature solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime (340.0 mg, 0.701mmol) in methylene chloride (8.0 mL) was added solid 1,1' carbonyl diimidazole (290.0 mg, 1.79 mmol) and sodium acetate (480.0 mg, 5.85 mmol). The resulting solution was stirred for 1.5 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then concentrated in vacuo and the resulting residue was directly applied to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a white solid (262 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (app q, J = 7.4 Hz, 1H), 7.52 (app tt, J = 8.4, 6.3 Hz, 1H), 7.14 (app dd, J = 8.6, 7.4 Hz, 2H), 6.94 (app dt, J = 8.5, 2.5 Hz, 1H), 6.88 (app dt, J = 8.5, 2.4 Hz, 1H), 5.43 (s, 2H),

2.32 (s, 3H); LC/MS C-18 column, t_r = 2.95 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). IR (neat) 3111, 3067, 3032, 2914, 2840, 2215 (nitrile stretch), 1678, 1587, 1470 cm $^{-1}$; ES-MS m/z 467 (M+H). ES-HRMS m/z 467.0037 (M+H calcd for $C_{20}H_{12}BrF_4N_2O_2$ requires 467.0013).

Example 567

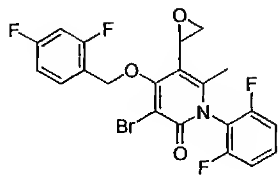


4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A solution of 4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (1.42 g, 3.50 mmol) in 1,2 dichloroethane (18 mL) was treated with solid N-iodosuccinimide (1.59 g, 7.06 mmol) and dichloroacetic acid (0.260 g, 2.01 mmol). The resulting solution was stirred and heated to 50 °C for 2.5 hours until complete consumption of starting material by LCMS. At this time the reaction was diluted with ethyl acetate (400 mL) and washed with sodium sulfite (5 % aqueous solution, 100 mL) and brine (3 X 200 mL). The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 30 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1.49 g, 82 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (app d, J = 6.8 Hz, 2H), 7.51-7.38 (m, 4H), 7.09 (app t, J = 8.0 Hz, 2H), 5.20 (s, 2H), 2.39 (s, 3H); LC/MS C-18 column, t_r = 3.28 minutes (5 to 95% acetonitrile/water over 5

minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 532 (M+H). ES-HRMS m/z 531.9196 (M+H calcd for $C_{19}H_{14}BrF_2INO_2$ requires 531.9215).

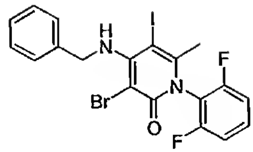
Example 568



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-oxiran-2-ylpyridin-2(1H)-one

Step 1: A sample of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one (10.0 mg, 0.0214 mmol) was treated with a solution of dimethyl dioxirane in acetone (approx. 0.1 M, 5 mL, 0.5 mmol). The reaction vessel was capped and sealed, and the resulting solution was stirred 6.0 hours. At this time the reaction was concentrated in vacuo and the resulting residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (4:6) to furnish a semi-solid (5.0 mg, 48 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (app q, J = 7.4 Hz, 1H), 7.46 (app tt, J = 8.5, 6.2, 1H), 7.11 (app t, J = 8.0 Hz, 2H), 6.94(app t, J = 8.2 Hz, 1H), 6.83 (app t, J = 9.2 Hz, 1H), 5.31 (AB-q, J = 10.9 Hz, Δ= 29.0 Hz, 2H), 3.63 (app t, J = 3.5 Hz, 1H), 3.03 (dd, J = 9.4, 5.0, 1H), 2.85 (dd, J = 5.2, 2.7, 1H), 2.14 (s, 3H); LC/MS C-18 column, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 484 (M+H) and 502 ($M+H_3O$). ES-HRMS m/z 502.0273 ($M+H_3O$ calcd for $C_{21}H_{17}BrF_4NO_4$ requires 502.0272).

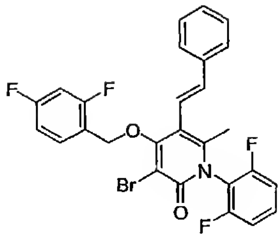
Example 569



4-(benzylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A slurry of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (80.0 mg, 0.141 mmol) and benzyl amine (300 mg, 2.80 mmol) was heated to 63 °C and stirred for 1.0 hours until complete disappearance of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (300 mL) and brine washed (3 X 200 mL). The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to a residue that was then subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a brown solid (60.0 mg, 81 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.22 (m, 6H), 7.04 (app t, J = 8.4 Hz, 2H), 5.02 (br t, J = 1.6 Hz, 1H), 4.86 (d, J = 5.5 Hz, 2H), 2.37 (s, 3H); LC/MS C-18 column, t_r = 3.02 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 531 (M+H). ES-HRMS m/z 530.9344 (M+H calcd for $C_{19}H_{15}BrF_2IN_2O$ requires 530.9375).

Example 570

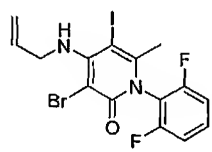


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-[(E)-2-phenylethenyl]pyridin-2(1H)-one

Step 1: To an anhydrous -78 °C solution of β-bromostyrene (1.80 g, 10.0 mmol) in ether (18 mL) was added sequentially a solution of zinc chloride (10.0 mL, 1.0 M ether, 10.0 mmol) over 1.0 minute and a solution of tert-butyl lithium (15.0 mL, 1.6 M pentanes, 24.0 mmol) over 8.0 minutes. The resulting solution became cloudy and the reaction mixture was allowed to warm to room temperature on its own accord (over 30 minutes). After an additional 1.0 hour, the suspension was transferred by syringe directly to a separate vessel containing a solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.50 g, 2.64 mmol) and tetrakis(tripheylphosphine)palladium (294 mg, 0.254 mmol) in anhydrous THF (4 mL). This resulting suspension was heated to 55 °C for 40 minutes and cooled to room temperature, whereby it was stirred under a positive pressure of argon for an additional 4.0 hours until complete disappearance of starting material by LCMS analysis. The reaction suspension was subsequently treated with $NaHCO_3$ and brine (100 and 200 mL, respectively). The resulting emulsion was extracted with ethyl acetate (3 X 300 mL) and the organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to a residue that was then subjected to SiO_2 chromatography with ethyl

acetate/hexanes (3:7) to furnish a reddish solid (1.25 g, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.39 (m, 2H), 7.38-7.24 (m, 5H), 7.10 (app t, J = 8.5 Hz, 2H), 6.84 (d, J = 17.2 Hz, 1H), 6.82-6.75 (m, 1H), 6.74-6.68 (m, 1H), 6.69 (d, J = 17.2, 1H), 5.11 (br s, 2H), 2.15 (s, 3H); LC/MS C-18 column, t_r = 3.74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 544 (M+H). ES-HRMS m/z 544.0565 (M+H calcd for $C_{27}H_{19}BrF_4NO_2$ requires 544.0530).

Example 574

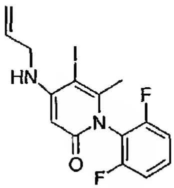


4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A slurry of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.40 g, 2.46 mmol) and allyl amine (1.98 mg, 34.6 mmol) was heated to 50 °C and stirred for 1.0 hours until complete disappearance of starting material by LCMS analysis. The reaction mixture was then concentrated in vacuo (1.0 mm Hg) for 2 days at 50 °C to furnish a brown solid (1.18 g, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (app tt, J = 8.4, 6.2, 1H), 7.09 (app t, J = 8.4 Hz, 2H), 6.02 (app dq, J = 11.0, 6.2 Hz, 1H), 5.39 (dd, J = 16.9, 1.8 Hz, 1H), 5.30 (dd, J = 11.0, 1.8 Hz, 1H), 4.84 (br s, 1H), 4.35 (br s, 2H), 2.42 (s, 3H); LC/MS C-18 column, t_r =

2.71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 481 (M+H). ES-HRMS m/z 480.9261 (M+H calcd for $C_{15}H_{13}BrF_2IN_2O$ requires 480.9219).

Example 575

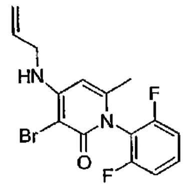


4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A solution of 4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.00 g, 2.07 mmol) and tetrakis(tripheylphosphine)palladium (420 mg, 0.363 mmol) in anhydrous THF (10 mL) under an argon stream was heated to 64 °C and stirred for 12 hours until complete disappearance of starting material by LCMS analysis. The reaction suspension was subsequently treated with brine (600 mL). The resulting emulsion was extracted with ethyl acetate (3 X 400 mL) and the organic extracts were anhy. Na_2SO_4 dried, filtered, and concentrated in vacuo to a residue that was then subjected to SiO_2 chromatography with ethyl acetate/hexanes (gradient 3:7) to furnish a solid (376 mg, 45 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.55 (app tt, J = 8.7, 6.3, 1H), 7.18 (app t, J = 7.6 Hz, 2H), 5.89 (app ddd, J = 15.4, 10.3, 5.1 Hz, 1H), 5.01 (app d, J = 17.0, Hz, 1H), 5.50 (s, 1H), 5.22 (app d, J = 11.0 Hz, 1H), 4.35 (app d, J = 5.0 Hz , 2H), 2.36 (s, 3H); LC/MS C-18 column, t_r = 2.33 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection

254 nm, at 50°C). ES-MS m/z 403 (M+H). ES-HRMS m/z 403.0133 (M+H calcd for $C_{15}H_{14}F_2IN_2O$ requires 403.0113).

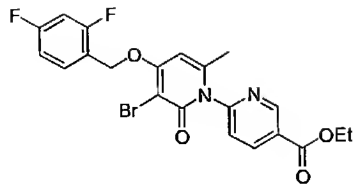
Example 576



4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)- one (197 mg, 0.445 mmol) and allyl amine (1.32 mg, 23.1 mmol) in THF (6.0 mL) was heated to 68 °C and stirred for 74.0 hours. The reaction mixture was then concentrated in vacuo (30 mm Hg) to furnish a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a solid (36.0 mg, 23 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.55 (app tt, J = 8.5, 6.5, 1H), 7.18 (app t, J = 8.5 Hz, 2H), 6.14 (s, 1H), 5.91 (app dq, J = 11.5, 6.4 Hz, 1H), 5.23 (dd, J = 17.0, 1.5 Hz, 1H), 5.19 (dd, J = 11.0, 1.6 Hz, 1H), 4.00 (app d, J = 4.7 Hz , 2H), 1.98 (s, 3H); LC/MS C-18 column, t_r = 2.24 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 355 (M+H). ES-HRMS m/z 355.0257 (M+H calcd for $C_{15}H_{14}F_2BrF_2N_2O$ requires 355.0252).

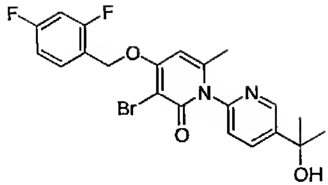
Example 577



ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2H-1,2'-bipyridine-5'-carboxylate

Step 1: To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (500.0 mg, 1.51 mmol) and Cs_2CO_3 (1.50 g, 4.60mmol) in 1-methyl-2-pyrrolidinone (3.0 mL) was added ethyl 6-chloronicotinate (900 mg, 4.85 mmol). The resulting suspension was stirred and heated to 106 °C for 36 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a solid. ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.68 (app d, J = 2.5 Hz, 1H), 8.39 (dd, J = 8.7, 2.3 Hz, 1H), 7.62 (app q, J = 8.2 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.08 (s, 1H), 7.08-6.99 (m, 2H), 5.31 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); LC/MS C-18 column, t_r = 3.44 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 479 (M+H). ES-HRMS m/z 479.0401 (M+H calcd for $C_{21}H_{18}BrF_2N_2O_4$ requires 479.0431).

Example 578

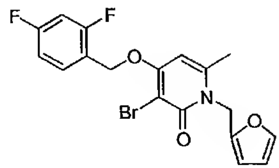


3-bromo-4-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-6-methyl-2H-1,2'-bipyridin-2-one

Step 1: To a 0 °C solution of methyl magnesium bromide (3.0 M, 3.5 mL, 10.5 mmol) was added dropwise over 15 minutes a solution of ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2H-1,2'-bipyridine-5'-carboxylate (500.0 mg, 1.05 mmol) in THF (4.0 mL). The internal temperature of the reaction was never allowed to exceed 0 °C. The resulting solution was maintained for 30 minutes until complete consumption of starting material by LCMS analysis. Next, a solution of ammonium chloride (saturated aqueous, 160 mL) was added. The reaction mixture was extracted with ethyl acetate (3 X 100 mL) and the resulting organic extracts were separated, Na_2SO_4 dried, and concentrated in vacuo to a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes (gradient 3:7 to 6:4) to furnish a solid (386 mg, 79 %). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.23 (app d, J = 2.8 Hz, 1H), 7.97 (dd, J = 8.6, 2.3 Hz, 1H), 7.61 (app q, J = 8.2 Hz, 1H), 7.06-7.00 (m, 3H), 7.00 (s, 1H), 5.30 (s, 2H), 2.38 (s, 3H), 1.54 (s, 6H); LC/MS C-18 column, t_r = 2.75 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 465 (M+H). ES-HRMS m/z 465.0615 (M+H calcd for $C_{21}H_{20}BrF_2N_2O_3$ requires 465.0620). IR(neat) 3366, 3030, 2974, 1600, 1507, 1362, 1232 cm $^{-1}$. ^{13}C NMR (400 MHz, d_4-MeOH, visible peaks with carbon fluorine coupling present) δ 164.4, 160.7, 158.9, 157.6, 143.6, 141.6, 137.5,

131.61, 131.56, 131.51, 131.46, 119.29, 119.25, 119.15, 119.11, 112.23, 111.55, 111.52, 111.33, 111.29, 106.0, 103.9, 103.7, 103.4, 96.8, 70.3, 64.9, 64.8, 30.5, 22.6.

Example 579

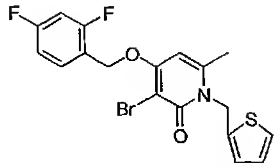


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-furylmethyl)-6-methylpyridin-2(1H)-one

Step 1: Preparation of the title compound . To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330.0 mg, 1.00 mmol)) and NaH (48.0 mg, 2.0 mmol) in THF (3.0 mL) was added 2-(chloromethyl)furan (461 mg, 3.97 mmol). The resulting suspension was stirred and heated to 68 °C for 9 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (4:6) to furnish a solid. ^1H NMR (300 MHz, d_4-MeOH) δ 7.62 (app q, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.06 (app t, J = 8.7 Hz, 2H), 6.51 (s, 1H), 6.41-6.37 (m, 2H), 5.37 (s, 2H), 5.32 (s, 2H), 2.61 (s, 3H); LC/MS C-18 column, t_r = 2.63 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 410 (M+H).

ES-HRMS m/z 410.0177 (M+H calcd for $C_{18}H_{15}BrF_2NO_3$ requires 410.0198).

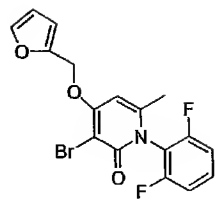
Example 580



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(thien-2-ylmethyl)pyridin-2(1H)-one

Step 1: To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330.0 mg, 1.00 mmol)) and NaH (48.0 mg, 2.0 mmol) in THF (3.0 mL) was added 2-(chloromethyl)thiophene (461 mg, 3.97 mmol). The resulting suspension was stirred and heated to 68 °C for 12 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (4:6) to furnish a solid. ^1H NMR (400 MHz, d_4-MeOH) δ 7.58 (app q, J = 8.2 Hz, 1H), 7.30 (app dd, J = 5.1, 1.2 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 7.01 (app t, J = 8.1 Hz, 2H), 6.93 (dd, J = 5.1, 3.4 Hz, 1H), 6.43 (s, 1H), 5.49 (s, 2H), 5.25 (s, 2H), 2.51 (s, 3H); LC/MS C-18 column, t_r = 2.74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 426 (M+H). ES-HRMS m/z 425.9936 (M+H calcd for $C_{18}H_{15}BrF_2NO_2S$ requires 425.9969).

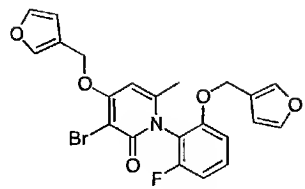
Example 581



3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one

Step 1: To a suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)- one (250 mg, 0.445 mmol) and furfuryl alcohol (198 mg, 2.0 mmol) in THF (2.5 mL) was added solid NaH (46.0 mg, 1.92 mmol). Following the evolution of gas, the resulting suspension laws heated to 60 °C and stirred for 3.5 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ammonium chloride (saturated aqueous, 100 mL) and extracted with ethyl acetate (3 X 100 mL). The resulting organic extracts were separated, Na_2SO_4 dried, and concentrated to provide a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a solid (110.0 mg, 49 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.63 (app tt, J = 8.5, 6.2, 1H), 7.62-7.61 (m, 1H), 7.28 (app t, J = 8.5 Hz, 2H), 6.77 (s, 1H), 6.68 (d, J = 4.1 Hz, 1H), 6.51(dd, J = 4.2, 3.9 Hz, 1H), 5.34 (s, 2H), 2.15 (s, 3H); LC/MS C-18 column, t_r = 2.43 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 396 (M+H). ES-HRMS m/z 396.0044 (M+H calcd for $C_{17}H_{13}BrF_2NO_3$ requires 396.0041).

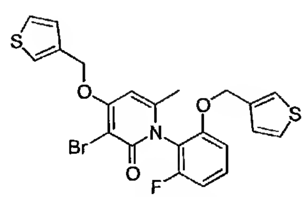
Example 582



3-bromo-1-[2-fluoro-6-(3-furylmethoxy)phenyl]-4-(3-furylmethoxy)-6-methylpyridin-2(1H)-one

By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one (Example 581) and substituting 3-furylmethanol for furfuryl alcohol, the title compound was prepared in 55 % chemical yield. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.64 (s, 1H), 7.55-7.42 (m, 3H), 7.40 (app t, J = 1.4 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 6.92 (app t, J = 8.4 Hz, 1H), 6.58 (s, 2H), 6.34 (br s, 1H), 5.21 (s, 2H), 5.03 (AB-q, J = 14.0 Hz, Δ= 58.0 Hz, 2H), 1.99 (s, 3H); LC/MS C-18 column, t_r = 2.67 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 474 (M+H). ES-HRMS m/z 474.0346 (M+H calcd for $C_{22}H_{18}BrFNO_5$ requires 474.0347).

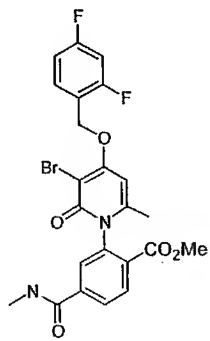
Example 583



3-bromo-1-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-6-methyl-4-(thien-3-ylmethoxy)pyridin-2(1H)-one

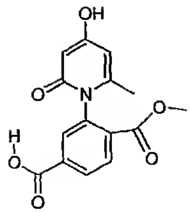
By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one Example 581 and substituting thien-3-ylmethanol for furfuryl alcohol, the title compound was prepared in 38 % chemical yield. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.50-7.42 (m, 3H), 7.33 (dd, J = 5.0, 3.0 Hz, 1H), 7.26 (br d, J = 2.0 Hz, 1H), 7.19 (dd, J = 5.0, 1.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.98 (dd, J = 14.9, 1.3 Hz, 1H), 6.93 (dt, J = 8.7, 1.0 Hz, 1H), 6.53 (br s, 1H), 5.33 (s, 2H), 5.14 (AB-q, J = 12.1 Hz, Δ= 50.0 Hz, 2H), 1.97 (s, 3H); LC/MS C-18 column, t_r = 2.93 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 506 (M+H). ES-HRMS m/z 505.9881 (M+H calcd for $C_{22}H_{16}BrFNO_3S_2$ requires 505.9890).

Example 584



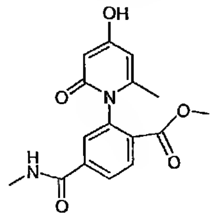
methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate

Step 1: Preparation of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid .



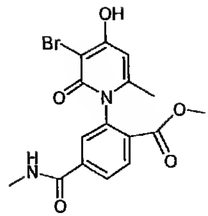
4-Hydroxy-6-methyl-2-pyrone (75.0 g, 595 mmol) and 3-amino-4-(methoxycarbonyl)benzoic acid (40.0 g, 0.205 mmol) were suspended in 56 ml of 1,2-dichlorobenzene in a 500 ml, 3-necked, round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 180 °C over a period of 26 minutes during which time all solids dissolved. Upon reaching an internal temperature of 180 °C, the reaction was allowed to maintain this temperature for an additional 25.0 minutes during which time the evolution of water from the reaction mixture was evident. Next, the heating apparatus was removed and the reaction was allowed to cool on its own accord to about 100 °C. The reaction was then diluted with 160 ml of toluene and stirred. After about 10 minutes, the reaction reached room temperature and a gummy solid had formed. The precipitate was filtered, washed with EtOAc (400 mL) and water (200 mL, 55 °C), and dried in vacuo to give a tan solid (30.5 g, 49%). ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.20-8.09 (m, 2H), 7.84 (s, 1H), 6.08 (app d, J = 1.0 Hz, 1H), 5.76 (app d, J = 2.3 Hz, 1H), 3.76 (s, 3H), 1.91 (s, 3H). LC/MS, C-18 column, t_r = 1.96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50 °C). ES-MS m/z 304 (M+H). ES-HRMS m/z 304.0803 (M+H calcd for $C_{15}H_{14}NO_6$ requires 304.0816).

Step 2: Preparation of methyl 2-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate .



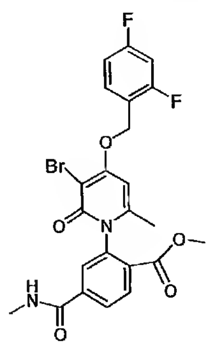
To a solution of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid (from Step 1) (1.00 g, 3.30 mmol) in dimethylformamide (10 mL) and THF (10 mL) was added cyclohexylcarbodiimide-derivatized silica gel (a product of Silicycle chemical division Quebec, Canada) with a loading of 0.60 mmol/g (15.2 g, 9.73 mmol). After stirring for 30 minutes, a solution of methylamine (2.0 M, THF, 2.9 mL, 5.8 mmol) was added followed by the addition of 1-hydroxy-benzotriazole (20.0 mg, 0.15 mmol). The reaction suspension was allowed to stir for 24 hours until the complete disappearance of starting material by LCMS analysis. The silica suspension was filtered and washed with 300 mL ethyl acetate/methanol (9:1) and 300 mL ethyl acetate/methanol (1:1). The resulting mother liquor was concentrated to furnish a brown semi-solid (898 mg, 86 %). ^{1}H NMR (300 MHz, d_4-MeOH) δ 8.22 (d, J = 8.0 Hz, 1H), 8.04 (dd, J = 8.3, 1.9 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 6.13 (d, J = 1.5, Hz, 1H), 5.80 (d, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.03 (s, 3H), 1.97 (s, 3H). LC/MS, C-18 column, t_r = 1.31 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 317 (M+H). ES-HRMS m/z 317.1142 (M+H calcd for $C_{16}H_{17}N_2O_5$ requires 317.1132).

Step 3: Preparation of methyl 2-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4- [(methylamino)carbonyl]benzoate .



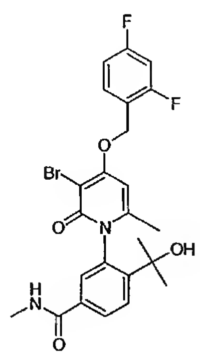
To a room temperature suspension of methyl 2-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate (from Step 2) (406.0 mg, 1.28 mmol) in CH_2Cl_2 (8 mL) was added solid N-bromosuccinimide (251 mg, 1.41 mmol) and stirred for 10 minutes until complete consumption of starting material by LCMS analysis. The reaction was next diluted with CH_2Cl_2 (5 mL), ethyl acetate (5 mL), and hexanes (1 mL). After approximately 30 minutes the resulting white precipitate was filtered and washed with ethyl acetate (5 mL) to furnish a solid (298 mg, 62%). ^1H NMR (400 MHz, d_4-MeOH) δ 8.20 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.69 (s, 1H), 6.18 (s 1H), 3.75 (s, 3H), 2.91 (s, 3H), 1.91 (s, 3H); LC/MS, t_r = 1.27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 395 (M+H). ES-HRMS m/z 395.0237 (M+H calcd for $C_{16}H_{16}BrN_2O_5$ requires 395.0237).

Step 4: Preparation of the title compound .



To a solution of methyl 2-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate (from Step 3) (241 mg, 0.610 mmol) in dimethylformamide (0.5 mL) was added sequentially K_2CO_3 (240 mg, 1.73 mmol) and 2,4 difluorobenzyl bromide (0.085 mL, 0.66 mmol). The resulting suspension was stirred for 6.5 hours until complete consumption of starting material by LCMS analysis. The reaction was then diluted with ethyl acetate (200 mL) and brine washed (3 X 200 mL). The resulting organic extract was Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 5 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected. ^1H NMR (400 MHz, d_4-MeOH) δ 8.22 (d, J = 8.2 Hz, 1H), 8.03 (dd, J = 8.2, 1.7 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.67 (app q, J = 8.3 Hz, 1H), 7.05 (app t, J = 8.6 Hz, 2H), 6.64 (s, 1H), 5.37 (s, 2H), 3.74 (s, 3H), 2.90 (s, 3H), 2.01 (s, 3H). LC/MS C-18 column, t_r = 2.87 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 521 (M+H). ES-HRMS m/z 521.0491 (M+H calcd for $C_{23}H_{20}BrF_2N_2O_5$ requires 521.0518).

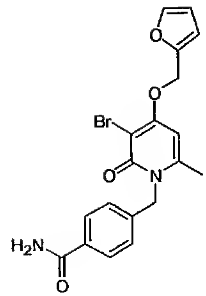
Example 585



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(1-hydroxy-1-methylethyl)-N-methylbenzamide

Step 1: To a -10 °C solution of methyl magnesium bromide (3.0 M, 0.60 mL, 1.8 mmol) was added dropwise over 10 minutes a solution of methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate (85.0 mg, 0.163 mmol) in THF (1.0 mL). The internal temperature of the reaction was never allowed to exceed 0 °C. The resulting solution was maintained for 10 minutes. Next, a solution of ammonium chloride (saturated aqueous, 100 mL) was added. The reaction mixture was removed from the bath and resulting emulsion was extracted with ethyl acetate (3 X 100 mL) and the resulting organic extracts were separated, Na_2SO_4 dried, and concentrated in vacuo to a residue that was subjected to SiO_2 chromatography with ethyl acetate/hexanes (gradient 3:7 to 6:4) to furnish a solid (16 mg, 19 %). ^1H NMR (400 MHz, d_4-MeOH) δ 7.89 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.61 (app q, J = 8.2 Hz, 1H), 7.41 (s, 1H), 7.03-6.99 (m, 2H), 6.57 (s, 1H), 5.30 (s, 2H), 2.83 (s, 3H), 2.05 (s, 3H), 1.51 (s, 3H), 1.39 (s, 3H); LC/MS C-18 column, t_r = 2.28 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 521 (M+H). ES-HRMS m/z 521.0860 (M+H calcd for $C_{24}H_{24}BrF_2N_2O_4$ requires 521.0882).

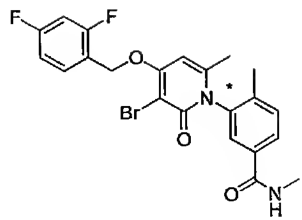
Example 586



3-bromo-1-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-6-methyl-4-(thien-3-ylmethoxy)pyridin-2(1H)-one

By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one Example 581 and substituting 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide for 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)- one , the title compound was prepared in 76 % chemical yield. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.83 (d, J = 8.1 Hz, 2H), 7.54 (app d, J = 1.1 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 6.57 (d, J = 3.2 Hz, 1H), 6.53 (s, 1H), 6.43 (dd, J = 3.1, 1.8 Hz, 1H), 5.45 (br s, 2H), 5.22 (s, 2H), 2:34 (s, 3H); LC/MS C-18 column, t_r = 1.98 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 417 (M+H). ES-HRMS m/z 417.0469 (M+H calcd for $C_{19}H_{18}BrN_2O_4$ requires 417.0444).

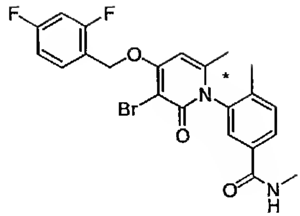
Example 587



(-)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

Example 489 (1.78 g, 4.36 mmol) were separated using a Chiral Technologies Chiralpak AD column (21 mm x 250 mm, 20 μm) eluting with 100% ethanol (isocratic, 20 ml/min), loading 10 mg per injection. Fractions of the early-eluting atropisomer were pooled and concentrated in vacuo to the title compound (718 mg, 80%). Analytical chiral LC (Chiralpak AD, 4.6 mm x 50 mm, 10μm particle size, 0.5 ml/min ethanol) Retention time: 1.70 min, ee 94%. $[\alpha]_D$ = -23.8° (5 mg/ml DMSO, 22 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (br qr, J = 4.51 Hz, 1H), 7.82 (dd, J = 7.92, 1.70 Hz, 1H), 7.68 (dt, J = 8.24, 6.58 Hz, 1H), 7.58 (d, J = 1.59 Hz, 1H), 7.48 (d, J = 7.98 Hz, 1H), 7.34 (dt, J = 9.90, 2.50 Hz, 1H), 7.18 (dt, J = 8.53, 2.57 Hz, 1H), 6.71 (s, 1H), 5.33 (s, 2H), 2.74 (s, 3H), 1.98 (s, 3H), 1.88 (s, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.58 (quintet, J = 7.49 Hz, 1F), -113.65 (quartet, J = 9.11 Hz, 1F). ES-HRMS m/z 477.0612 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_3$ requires 477.0620).

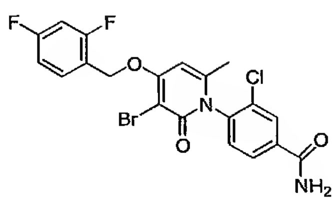
Example 588



(+)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

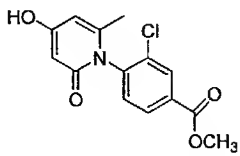
The title compound was prepared as in Example 587 , pooling the late-eluting atropisomer (722 mg, 81%). Analytical chiral LC (Chiralpak AD, 4.6 mm x 50 mm, 10μm particle size, 0.5 ml/min ethanol) Retention time: 2.00 min, ee 98%. $[\alpha]_D$ = +28.2° (5 mg/ml DMSO, 22 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (br qr, J = 4.51 Hz, 1H), 7.82 (dd, J = 7.92, 1.70 Hz, 1H), 7.68 (dt, J = 8.24, 6.58 Hz, 1H), 7.58 (d, J = 1.59 Hz, 1H), 7.48 (d, J = 7.98 Hz, 1H), 7.34 (dt, J = 9.90, 2.50 Hz, 1H), 7.18 (dt, J = 8.53, 2.57 Hz, 1H), 6.71 (s, 1H), 5.33 (s, 2H), 2.74 (s, 3H), 1.98 (s, 3H), 1.88 (s, 3H). ^{19}F-NMR (400 MHz, DMSO-d_6) δ -109.58 (quintet, J = 7.49 Hz, 1F), -113.65 (quartet, J = 9.11 Hz, 1F). ES-HRMS m/z 477.0614 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_3$ requires 477.0620).

Example 589



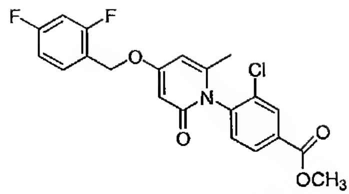
4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzamide

Step 1: Preparation of methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate .



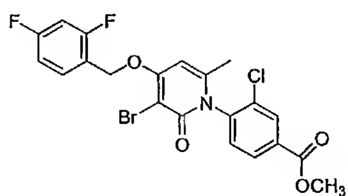
4-Hydroxy-6-methyl-2-pyrone (24.5 g, 193.9 mmol) and methyl-3-amino-2-chlorobenzoate (30 g, 161.6 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 175°C for 20 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 110°C. At this point, 200 ml of toluene was added. The toluene mixture was allowed to stir for 72 hours at room temperature. A precipitate was collected on a filter pad. The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C. water to remove excess pyrone, and dried in vacuo to give a tan solid (13.0 g, 27% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.26 (d, J = 1.81 Hz, 1H), 8.14 (dd, J = 8.26, 1.81 Hz, 1H), 7.54 (d, J = 8.26, Hz, 1H), 6.14(dd, J = 2.42, 1.0 Hz, 1H), 5.83 (d, J = 2.42 1H), 4.00 (s, 3H), 1.96 (s, 3H); LC/MS, t_r = 1.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

Step 2: Preparation of methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



Methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (from Step 1) (2.4g, 8.17 mmol) was taken up in DMF (10 ml). 2,4-difluorobenzylbromide (1.05 ml, 8.17 mmol) and K_2CO_3 (1.13 g, 8.17 mmol) were added. The reaction stirred for 6 hours at room temperature. At this time, the reaction was poured into water (200 ml) and extracted with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4, filtered, and the solvent removed in vacuo to give amber oil (2.62 g, 77% crude yield). LC/MS, t_r = 2.79 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

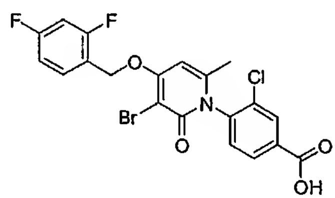
Step 3: Preparation of methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate .



Methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 2) (2.60g, 6.21 mmol) was taken up in CH_2Cl_2 (20 ml). N-bromosuccinimide (1.11g, 6.21 mmol) was added and the mixture stirred at room temperature for 4 hours. The CH_2Cl_2 is removed in vacuo and

the residue is taken up in CH_3CN. The resulting precipitate is collected on a filter pad and washed with CH_3CN to yield a white solid (0.75 g, 24%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 1.88 Hz, 1H), 8.06 (dd, J = 8.19, 1.75 Hz, 1H), 7.59 (app q, J = 8.46 Hz, 1H), 7.33 (d, J = 8.19, 1H), 6.96 (dt, J = 8.06, 1.21 Hz, 1H), 6.89 - 6.84 (m, 1H), 6.13 (s, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 1.95 (s, 3H); ES-MS m/z 478 (M+H). ES-HRMS m/z 497.9892 (M+H calcd for $C_{22}H_{16}BrClF_2NO_4$ requires 497.9914).

Step 4: Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoic acid.

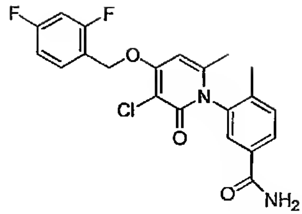


Methyl-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate (2.30g, 4.61 mmol) was taken up in THF (20 ml) and H_2O (4 ml). 2.5 N NAOH (9.2 ml) was added to the vessel and the reaction stirred overnight to completion. Concentrated HCl was added dropwise until reaction was made acidic (pH = 1). H_2O (100 ml) and THF (100 ml) were added to the mixture. The contents were poured into a separatory funnel and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, the solvent removed in vacuo, and the residue was taken up in a 50% mixture of ethyl acetate/hexane. The precipitate was collected on a filter pad to yield a white powder (1.5g, 67%). ^1H NMR (300 MHz, DMSO) δ 13.59 (1H), 8.16 (d, J = 1.81 Hz, 1H),

8.06 (dd, J = 6.24, 1.81 Hz, 1H), 7.73 (app q, J = 8.46, 1H), 7.68 (d, J = 8.26 Hz, 1H), 7.38 (dt, J = 9.48, 2.62 Hz, 1H) 7.26 - 7.18 (m, 1H), 6.80 (s, 1H), 5.39 (s, 2H), 3.93 (s, 3H), 1.96 (s, 3H); ES-MS m/z 483 (M+H). ES-HRMS m/z 483.9749 (M+H calcd for $C_{20}H_{14}BrClF_2NO_4$ requires 483.9757).

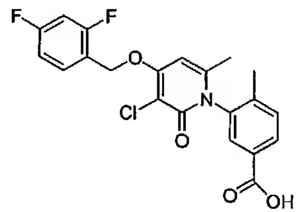
Step 5: 4-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoic acid (0.5 g, 1.03 mmol) was taken up in THF (10 ml). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0.22 g, 1.24 mmol) and N-methyl morpholine (0.34 ml, 3.09 mmol) were added. The mixture stirred at room temperature for 1 hour. At this time, NH_4OH (2.5 ml) was added and the reaction stirred at room temperature for one more hour. To the reaction mixture was added more THF (50 ml) and water (200 ml). The mixture was extracted with ethyl acetate. The ethyl acetate extraction was washed with saturated brine solution. The brine layer was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was taken up in ethyl acetate and the resulting precipitate was collected on a filter pad to yield a white powder (0.38 g, 76%) ^1H NMR (300 MHz, CD_3OD) δ 8.18 (d, J = 1.81 Hz, 1H), 8.02 (dd, J = 8.26, 2.01 Hz, 1H), 7.69 (app q, J = 8.26 Hz, 1H), 7.55 (d, J = 8.06 Hz, 1 H) 7.12 - 7.06 (m, 2H), 6.71 (s, 1H), 5.40 (s, 2H), 2.07 (s, 3H). ES-MS m/z 482 (M+H). ES-HRMS m/z 482.9919 (M+H calcd for $C_{20}H_{15}BrClF_2N_2O_3$ requires 482.9917).

Example 590



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(H)-yl]-4-methylbenzamide

Step1: Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .

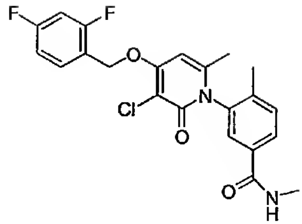


3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from above) (7.5g,19.4 mmol) and NCS (2.6 g, 19.4 mmol) were taken up in 65°C dichloroethane (100 ml). A catalytic amount of dichloroacetic acid (2 drops) was added. After two hours the solvent was removed in vacuo and the residue was taken up in diethyl ether. The precipitate was collected on a filter pad and then taken up in 50% ethyl acetate/hexanes to remove residual succinimide. The precipitate was collected on a filter pad and then dried in vacuo to produce a white powder (4.2 g, 52%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.10 (dd, J = 7.85, 1.81 Hz, 1H), 7.83 (d, J = 8.26, 1.81 Hz, 1H), 7.40 (app q, J = 8.26 Hz, 1H), 7.58 (d, J = 7.85 Hz, 1H), 7.13 - 7.06 (m, 2H), 6.74 (s, 1H), 5.40 (s, 2H), 2.14

(s, 3H), 2.04 (s, 3H); ES-MS m/z 420 (M+H). ES-HRMS m/z 420.0786 (M+H calcd for $C_{21}H_{17}ClF_2NO_4$ requires 420.0809).

Step 2: 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (1.5g, 3.57 mmol) was taken up in THF (30 ml). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0.75 g, 4.28 mmol) and N-methyl morpholine (1.18 ml, 10.72 mmol) were added. The mixture stirred at room temperature for 1 hour. At this time, NH_4OH (7.5 ml) was added and the reaction stirred at room temperature for one more hour. To the reaction mixture was added more THF (100 ml) and water (150 ml). The mixture was extracted with ethyl acetate. The ethyl acetate extraction was washed with saturated brine solution. The brine layer was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was taken up in ethyl acetate and the resulting precipitate was collected on a filter pad to yield a white powder (1.32 g, 88%) ^1H NMR (300 MHz, CD_3OD) δ 7.96 (dd, J = 7.85, 1.81 Hz, 1H), 7.71 (d, J = 1.81 Hz, 1H), 7.67 (app q, J = 8.06 Hz, 1H), 7.56 (d, J = 8.06 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.74 (s, 1H), 5.40 (s, 2H), 2.13 (s, 3H) 2.05 (s, 3H). ES-MS m/z 419 (M+H). ES-HRMS m/z 419.0979 (M+H calcd for $C_{21}H_{18}ClF_2N_2O_3$ requires 419.0969).

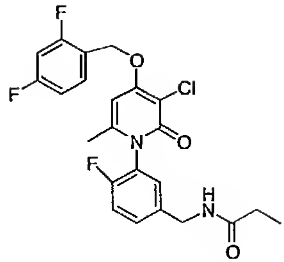
Example 591



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

The title compound was prepared from 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from step 1 above) (1.5 g, 3.57 mmol) in dichloromethane (35 ml). To this mixture, 2.0 M methyl amine in THF (3.6 ml, 7.14 mmol) was added, followed, in order, by EDCI (0.67 g, 4.28 mmol), 1-hydroxybenzotriazole (0.58 g, 4.28 mmol) and triethylamine (0.99 ml, 7.14 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate. The combined organic layer was then washed with saturated $NaHCO_3$ (aq.) and extracted 3 times with ethyl acetate. The organic layers were combined and washed with H_2O and extracted 3 times with ethyl acetate. The organic layers were combined and dried over Na_2SO_4 and evaporated. The resulting residue was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (1.5g, 72%). ^1H NMR (300 MHz, CD_3OD) δ 7.90 (dd, J = 8.06, 1.81 Hz, 1H), 7.67 (app q, J = 6.44 Hz, 1H), 7.55 (d, J = 8.06 Hz, 1H), 7.13 - 7.06 (m, 2H), 6.74 (s, 1H), 5.40 (s, 2H), 2.93 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H); ES-MS m/z 433 (M+H). ES-HRMS m/z 433.1153 (M+H calcd for $C_{22}H_{20}ClF_2N_2O_3$ requires 433.1125).

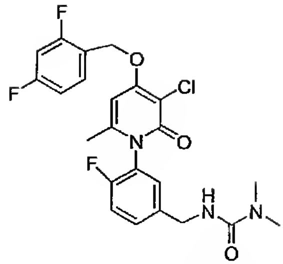
Example 592



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}propanamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.56 mmol), propionyl chloride (49 μL, 0.56 mmol), triethylamine (195 μL, 1.4 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. The reaction mixture was poured into a saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain (240 mg, 91%) as a yellow solid. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.3 (t, J = 5.8 Hz, 1H), 7.6 (q, J = 8.7 and 6.58 Hz, 1H), 7.38 (d, J = 7.78 Hz, 1H), 7.3 (dd, J = 2.6 and 7.6 Hz, 1H), 7.22 (d, J = 7.51 Hz, 1H), 7.12 (td, J = 2.0 and 6.5 Hz, 1H), 6.65 (s, 1H), 5.3 (s, 2H), 4.23 (d, J = 3.6 Hz, 2H), 2.1 (q, J = 7.7 Hz 2H), 1.98 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H) ppm. ES-HRMS m/z 465.1203 (M+H calcd for $C_{23}H_{21}ClF_3N_2O_3$ requires 465.1187).

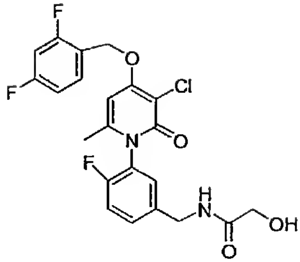
Example 593



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl} dimethylurea

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.56 mmol), dimethylcarbamyl chloride (52 µL, 0.56 mmol), triethylamine (195 µL, 1.4 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. The reaction mixture was poured into a saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain the desired product (245 mg, 86%) as a white solid. ^1H NMR (400 MHz, (CD_3OD) δ 7.61 (q, J = 7.9 and 6.7 Hz, 1H), 7.4(m, 1H), 7.3 (d, J = 9.3 Hz, 1H), 7.21 (m, 1H), 7.1 (m, 2H), 6.65 (s, 1H), 5.35 (s, 2H), 4.38 (s, 2H), 2.9 (s, 6H), 2.1 (s, 3H) ppm. ES-HRMS m/z 480.1269 (M+H calcd for $C_{23}H_{22}ClF_3N_3O_3$ requires 480.1296).

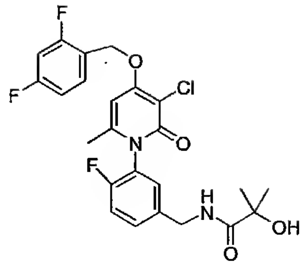
Example 594



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}-2-hydroxyacetamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.56 mmol), acetoxyacetyl chloride (66 µL, 0.62 mmol), triethylamine (195 µL, 1.4 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. NaOH (2.5M, 2.24 mmol, 1.0 mL) and MeOH (2.0mL) was added and stirred for 10 min to give the title compound. The reaction mixture was acidified with concentrated HCl and extracted with ethyl. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain (217 mg, 78%) of the desired product as a yellow solid. ^1H NMR (400 MHz, (CD_3OD) δ 7.6 (q, J = 7.6 and 6.9 Hz, 1H), 7.44 (m, 1H), 7.34 (m, 2H), 7.22 (m, 2H), 6.63 (s, 1H), 5.35 (s, 2H), 4.41 (s, 2H), 4.0 (s, 2H), 2.05 (s, 3H) ppm. ES-HRMS m/z 467.0957 (M+H calcd for $C_{22}H_{19}ClF_3N_2O_4$ requires 467.0980).

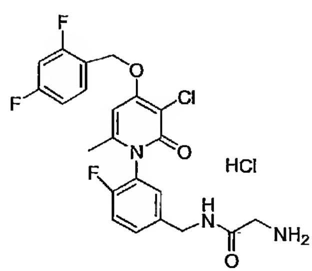
Example 595



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}-2-hydroxy-2-methylpropanamide

The title compound was prepared essentially as described in Example 594, with 1-chlorocarbonyl-1-methylethyl acetate substituting acetoxyacetyl chloride ^{1}H NMR (400 MHz, (CDCl$_3$) δ 9.9 (q, J = 8.2 and 6.5 Hz, 1H), 9.7 (t, J = 2.6 Hz, 1H), 9.5 (t, J = 8.9 Hz, 2H), 9.3 (m, 1H), 9.2 (m, 1H), 8.6 (s, 1H) 7.6 (s, 2H), 6.8 (d, J = 15 Hz, 1H), 6.63 (d, J = 15 Hz, 1H), 4.42 (d, J = 3.2 Hz, 6H), 3.99 (s, 3H) ppm. ES-HRMS m/z 495.1271 (M+H calcd for $C_{24}H_{23}ClF_3N_2O_4$ requires 495.1293).

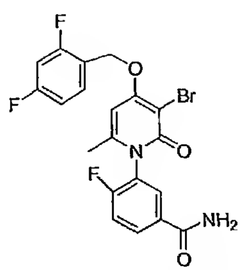
Example 596



N^1-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}glycinamide hydrochloride

A 25 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with boc-glycine (105 mg, 0.6 mmol) and 8 mL of DMF. The mixture was cooled to 0° C and isboutylchloroformate (77.5 µL, 0.6 mmol) was added and stirred for 20 min. 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.6 mmol) was added and stirred for 3h. After completion of the reaction by LC-MS, concentrated HCl (2 mL) and 2 mL of methanol was added to remove the boc group. The reaction was stirred for 24 h, neutralized with 2M NaOH and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain (196 mg, 66%) of the desired product as a the HCl salt. ^1H NMR (400 MHz, (CD_3OD) δ 7.6 (q, J = 8 and 6.5 Hz, 1H), 7.5 (m, 1H), 7.3 (m, 2H), 7.0 (m, 2H), 6.63 (s, 1H), 5.35 (s, 2H), 4.4 (q, J = 15 and 13.6 Hz, 2H), 3.7 (s, 2H), 2.05 (s, 3H) ppm. ES-HRMS m/z 466.1157 (M+H calcd for $C_{22}H_{20}ClF_3N_3O_3$ requires 466.1140).

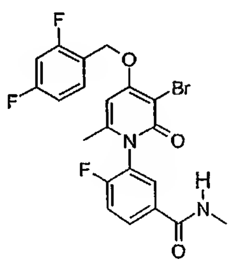
Example 597



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzamide

A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (3.65g, 7.8 mmol), 4-methylmorpholine (2.6 mL, 23.4 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.64g, 9.36 mmol) and tetrahydrofuran (40 mL). After stirring the mixture for 30 min at 25° C, NH_4OH (20.0 mL) was added. The mixture was stirred for 30 min and diluted with water. The product precipitated from solution. The precipitated was filtered and washed with water and diethyl ether to give the title compound (2.37g, 65%) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.9 (d, J = 7.3 Hz, 1H), 7.61 (q, J = 8.6 and 6.7 Hz, 1H), 7.5 (m, 2H), 7.3 (t, J = 9.6 Hz, 1H), 7.15 (t, J = 8.7 Hz, 1H), 6.7 (s, 1H), 5.36 (s, 2H), 2 (s, 3H) ppm. ES-HRMS m/z 469.0172 (M+H calcd for $C_{20}H_{15}BrF_3N_2O_3$ requires 469.0195).

Example 598



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-methylbenzamide

A solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (1 g, 2.1 mmol) in N,N-dimethylformamide (20 mL) was cooled to -10 C. Isobutyl chloroformate (0.27 mL, 2.1 mmol) and N-methyl morpholine (0.23 mL, 2.1 mmol) were added to the reaction